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WOMEN'S HOSPITAL



HARVARD
MEDICAL SCHOOL
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CCS ASSOCIATES

Evaluation of the Process for Collection, Classification, and Analysis of Safety Data Across NIH-sponsored Clinical Trials (CTSA)

Final Report

CCS Associates

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I. Summary

The Cross-Trial Safety Analysis (CTSA) project provided a unique opportunity to examine the process for collection, classification and analysis of safety data across several investigational sponsored clinical trials. This work was a continuation of the analysis of pooled and adjudicated safety data conducted for two of the CTSA studies in 2004–2005. This collaborative effort between the National Cancer Institute (NCI), Brigham and Women’s Hospital’s (BWH’s) Clinical Endpoint Committee (CEC), Statistics Collaborative, Inc (SCI), and CCS Associates (CCSA) was initiated on April 29, 2005. All these organizations had contributed to the initial pooled safety analysis and had extensive experience in performing the tasks carried under this project. Drs. Solomon (BWH/CEC) and Dr. Wittes (SCI), the lead investigators conducting the initial pooled analysis, also led the effort under the CTSA project.

This effort entailed organization, collection and analysis of safety data provided by six Celecoxib-sponsored studies through development of standard operating procedures (SOPs) and processes to achieve the goals of the project as outlined below. These studies included three NCI/NCI Canada studies (APC, Selenium, MA27), one National Institute of Aging (NIA)-sponsored study (ADAPT), one National Eye Institute (NEI)-sponsored trial, and one private industry (Pfizer)-sponsored study (Pre-SAP). These studies as listed in Table 1 below, generally met the following criteria for the proposed meta safety data analysis: over 500 subjects enrolled, two years of treatment, and placebo-controlled.

This report below summarizes the project specific objectives, provides a description of the approach in meeting the project goals, outlines the project challenges and outcomes, and presents project timelines and accomplishments under each specific task.

II. CTSA Project Objectives

Serious adverse events (SAEs) observed in several clinical trials using similar interventions have alerted NIH to the possible need for a higher level of oversight and safety monitoring for such trials. Goals of the CTSA were to evaluate current procedures for the collection and reporting of safety data within selected studies conducted across the NIH and to suggest strategies to harmonize and standardize data collection, thereby facilitating the potential for data sharing across NIH-sponsored trials.

NIH supports and conducts many separate clinical trials and has in place policies and procedures for conducting these studies, including requiring oversight by Data Safety Monitoring Boards (DSMB) (*e.g.*, Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials approved by the NCI Executive Committee on June 22, 1999). Though the policy for monitoring safety does not currently include cross-trial communications among DSMBs, there has been a need to review the effectiveness of current oversight processes to sustain a high level of alertness for problems that are only apparent from a higher platform of oversight when several separate, but contemporaneous trials are investigating closely related drugs or substances. The goal is to review the current policy. For example, celecoxib, a cyclooxygenase-2 (COX-2) selective inhibitor, was approved by the US Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis and osteoarthritis in 1998 based on efficacy and safety data from short- and medium-term trials (primarily 12 or 24 weeks at 100 or 200 mg po bid or 200 mg po qd). In 1999, the FDA also granted accelerated marketing approval for celecoxib “to reduce the number of adenomatous colorectal polyps in FAP as an adjunct to usual care” (FDA, December 23, 1999). The cerebro- and cardiovascular (CCV) risks of this agent (and others within the same class) have yet to be fully characterized. Following Merck’s voluntary withdrawal of Vioxx (rofecoxib) due to potential CCV events on 9/30/2004 and FDA statement regarding halting of treatment in the NCI-sponsored Adenoma Prevention with Celecoxib (APC) trial on December 17, 2004, on February 17, 2005, advisors to the FDA met for three days attempting to evaluate the risks and benefits of COX-2 selective inhibitors. The committee agreed that cardiovascular risk associated with these agents represents a class effect that may or may not reflect toxicities that are associated with the broader class of non-steroidal antiinflammatory drugs (NSAIDs). Safety data that partially supported the committee's recommendations came from the NCI-sponsored APC trial.

The APC trial was designed to evaluate the efficacy of Celecoxib in patients with colonic adenomatous polyps following one and three years of 200 or 400 mg po bid treatment. This trial identified a significantly increased risk of serious cardiovascular events including cardiac-related death, nonfatal heart attack, stroke, and congestive heart failure in patients taking celecoxib. However, analyses of The Prevention of Sporadic Adenomatous Polyps (PreSAP) Trial, which was conducted in a similar cohort and also tested celecoxib, have not revealed an increased cardiovascular risk [1]. Data arising from these and other prospective, randomized, placebo-controlled trials testing the value of this agent for other indications provide unique opportunities to define the true risks of celecoxib exposure. NIH is uniquely poised to assess CCV risks associated with celecoxib exposure because three institutes are currently sponsoring or co-sponsoring five different prospective, double-blind placebo-controlled trials involving > 500 planned participants who are followed for at least two years of drug exposure (note that the NEI study had fewer subject, but the treatment exposure and the design met this criteria). A meta-analysis of these study results provides opportunities to evaluate the processes whereby these institutes gather, classify, and analyze safety data on NIH-sponsored trials. Specific questions that this evaluation might answer include the type(s) of documentation required to adequately report SAEs (*e.g.*, hospital discharge summaries, case report forms, or investigator reports); as well as to define, grade and categorize SAEs that occur. Harmonization of SAE documentation, classification, and analysis across institutes would have facilitated the NIH's recent efforts to quantify and communicate the magnitude of CCV risk posed by exposure to celecoxib on dozens of NIH-sponsored trials. Finally, these evaluations will confirm the robustness of current SAE evaluations on clinical trials conducted across NIH.

The CTSA project attempts to address the following questions as a baseline regarding oversight of the NIH clinical trials previously identified. The findings from this meta-analysis are also expected to identify appropriate changes to clinical trial review and data management more broadly.

Question #1: How are CCV safety data collected, categorized, and analyzed within selected studies conducted across NIH?

Question #2: How might CCV safety data be harmonized across NIH-sponsored trials, thereby facilitating the potential for data sharing?

Question #3: How might real-time data sharing be achieved (*e.g.*, among DSMBs) in order to protect patient safety in ongoing trials? Within an institute? Across institutes?

III. Approach

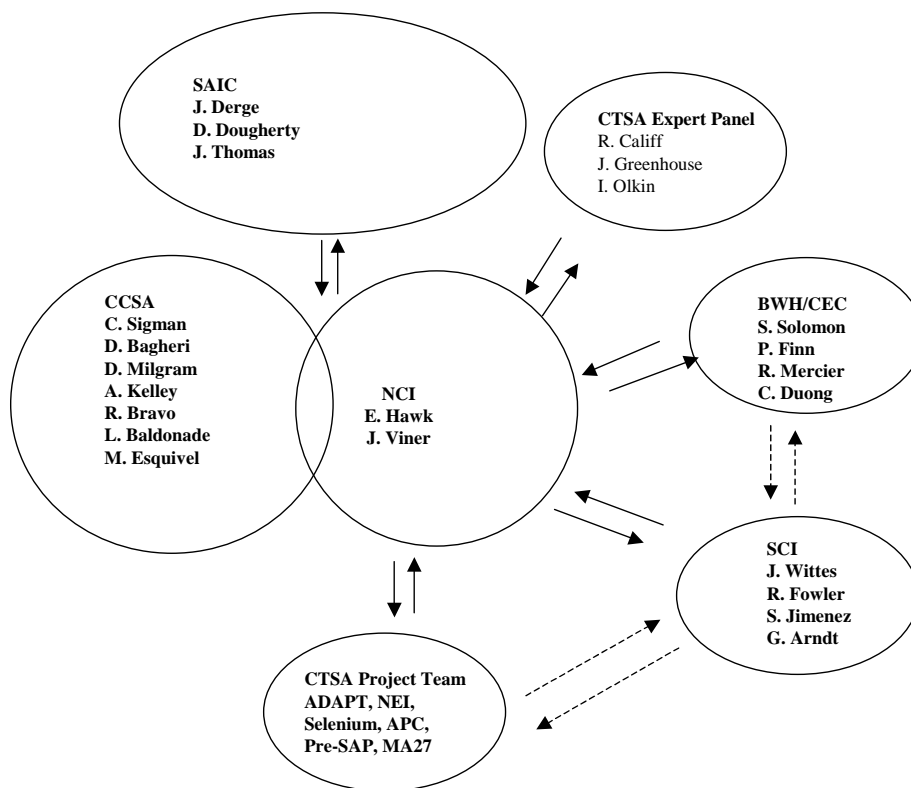
On December 17, 2004, NCI, Division of Cancer Prevention (DCP) instructed the investigators in charge of the DCP-sponsored studies with celecoxib to stop treatment as a result of APC trial Data Safety Monitoring Committee (DSMC) findings associated with higher risk of serious CCV events the active treated groups on the APC trial. These findings have been published by Solomon and colleagues [1]. These instructions were also forwarded to all other celecoxib NCI-sponsored studies and as a result, celecoxib treatment was also terminated for these studies. Therefore, in the interest of understanding the effect of celecoxib on CCV safety, NCI has asked the investigators from six studies (five sponsored by NIH, NCI Canada and one sponsored by Pfizer) listed below to cooperate in providing the available long-term data on the risk of CCV events among patients taking celecoxib. Details of these studies are provided in Table 1, below.

1. Adenoma Prevention with Celecoxib (APC) Trial
2. Prevention of Spontaneous Adenomatous Polyps (PreSAP) Trial
3. Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT)
4. Celecoxib and/or Selenium in Treating Patients with Adenomatous Colorectal Polyps (SelCel) Trial
5. Exemestane Compared with Anastrozole, with or without Celecoxib, in Treating Postmenopausal Women after Surgery for Primary Breast Cancer (MA27 Breast Adjuvant) Trial
6. Treatment of Diabetic Macular Edema Trial (03-EI-0065)

Project Team

In April 2005, a project entitled 'Evaluation of the Process for Collection, Classification, and Analysis of Safety Data Across NIH-sponsored Clinical Trials (CTSA)' was awarded to CCSA to participate in this collaborative effort. To accomplish the goals of the project, in addition to CCSA, several other organizations were involved in this effort; these were BWH's CEC and SCI; see Figure 1 below. All these organizations had previously contributed to the analysis of the safety data for the APC and Pre-SAP trials.

Figure 1: CTSA Project Team



*Each organization may communicate directly with CTSA Project Team based on their responsibilities.

The specific roles of each organization are described below:

CCSA

CCSA was responsible for providing coordination and administrative support to the project. These tasks include collecting and distributing documents and data listings as well as organizing and filing of the project data.

Specific activities included:

1. Created and maintained project team contact information; maintained project timeline.
2. Coordinated and communicated with the project team under NCI's direction.
3. Created templates for standardization/harmonization and collection of the required SAEs and study data for analysis.
4. Collected the SAEs based on the required CEC's selection.
5. Collected additional study data based on the required data points for analysis.
6. Collected and as necessary reviewed the supporting SAE documents (*e.g.*, case data information such as hospital discharge records).
7. Organized and maintained project files and collected data from the studies.
8. Prepared and submitted the SAE Screening Logs, SAE Shipment Logs, and Adjudication Shipment Logs to CEC.
9. Prepared the labeled-manila case folders; organized the required documents and shipped to CEC.
10. Communicated with the study sites; processed CCSA and CEC queries, as necessary.
11. Maintained tracking log files for the SAE Screening Logs, SAE Shipment Logs, and Adjudication Shipment Logs as well as the manilla case folders.
12. Developed and maintained a shadow file of the labeled-manilla case folders at CCSA.
13. Received and processed the Final Adjudication Forms.
14. Entered the Adjudication Forms data into the CTSA MS Access Database.
15. QC'd the data entered in MS Access Database.
16. Prepared CTSA Database in MS Access and sent to SCI for analysis.
17. Stored project documents, files, and electronic data.

BWH CEC

The CEC is based out of BWH and is comprised of the CEC Chairman, a Physician Reviewer, and administrative project staff. All members of the CEC are centrally located at BWH which allows for close, consistent collaboration on this project. The CEC was responsible for providing event review and adjudication services for the APC and Pre-SAP trials; therefore, it was logical for the same group to be responsible for providing the same services to other trials using celecoxib.

SCI

SCI, the statistical center for the CTSA project, had the primary responsibility for analysis of the data on the cardiovascular safety for each of the six clinical trials included in this analysis. To that end, it drafted a data analysis plan describing the planned statistical analyses for each trial and for the pooled analysis of all six trials. The pooled analysis was based on individual patient data. After the CTSA Steering Committee had agreed on the plan, SCI received data from the trials.

Each trial sent SCI baseline and follow-up data as agreed upon above as well as its randomization list. CCSA sent SCI the final CTSA database with all the required adjudicated endpoints. SCI merged the data from the various files into one SAS dataset.

The analysis proceeded by the following steps:

1. Prepared a spreadsheet summarizing each trial's method of collection of baseline variables.

2. For each trial, elicited information on how study drug was stopped and on follow-up of participants after they stopped study drug.
3. CTSA Steering Committee agreed upon definitions for “time on study” for each of the trials.
4. Created analysis datasets incorporating these definitions. Analysis datasets were sent to each individual trial’s Steering Committee for review.
5. The CTSA Steering Committee used uniform definitions of baseline variables (*e.g.*, race/ethnicity, cardio- and cerebrovascular risk factors).
6. Analyze each trial’s data in accordance with the analytic plan. It will send the results of those analyses, along with any SAS code requested by the CTSA Steering Committees, to each trial’s Steering Committee.
7. After each trial’s CTSA Study Representative has reviewed the analysis from its own trial, SCI to proceed with a pooled analysis.

SCI has quality assurance mechanisms in place to ensure the scientific and statistical validity of all its programs and reports. Statistical analyses, analytic programs, and data sets are all audited in conformance with SCI’s proprietary in-house *Data and Programming Guidelines*. SCI thoroughly reviews its reports for accuracy.

Janet Wittes, PhD assumed statistical leadership for SCI. Robert Fowler, MS, served as Project Manager and primary statistician. Gretchen Arndt served as Project Coordinator. She was responsible for collecting and summarizing the baseline data. Dr. Wittes, Mr. Fowler, and Ms. Arndt wrote the statistical report summarizing the results. Sara Jimenez, MS, wrote some of the SAS programs.

CTSA Expert Panel

In addition to the organizations (‘CTSA Working Group’) mentioned above, the CTSA Expert Panel, provided guidance to the Steering Committee by reviewing the project procedures particularly, the Statistical Plan in preparation for the data analysis. Also, this panel provided input on finalization of the final study report, as well as the manuscript prior to publication. Members of this panel were: 1. Robert Califf, MD, Duke Clinical Research Institute, Duke University Medical Center; 2. Joel Greenhouse, PhD, Department of Statistics, Carnegie Mellon University, and 3. Ingram Olkin, PhD, Department of Statistics, Stanford University (ret.).

Project Timeline

Between May 2005 and September 2007, representatives from CCSA, BWH CEC, SCI, and NCI, as well as representatives from each celecoxib study participated in regularly scheduled teleconferences to accomplish the goals of this project. All together, 52 individuals comprised the CTSA Project Team. On July 20, 2005, a face-to-face meeting was held to kick-off the project; 27 individuals attended the meeting, as presented in Appendix A. Several key issues including the Manual of Operations, Data Sharing policy and Confidentiality Agreement, Statistical Plan, and Project Timelines were discussed during the meeting. Minutes from this meeting are presented in Appendix B.

The overall project plan consisted of steps as outlined under each organization’s responsibilities presented above. The work initially was planned for six months, May–December, 2005. Due to challenges encountered during the course of this project, as described below, the timeline was re-adjusted in November 2005 with the project expected to be completed in September 2006 as displayed in Appendix C. Eventually, this timeline was pushed back by an additional year with a new project completion date of September 30, 2007.

Project Challenges

The CTSA project entailed collaborations of 6 study team members as well as the CTSA Working Group to meet the project's objectives. The table below presents the details for each study.

Table 1. List of Celecoxib Studies under CTSA Project							
Study	Sponsor	PI	Design/Cohort	Size	Dose	Duration	Objectives
Adenoma Prevention with Celecoxib (APC) Trial	NCI/Pfizer	Bertagnolli	Double-blind, randomized, aspirin stratified (up to 325 mg qod), multi-center, international adenoma patients	2000	200, 400, placebo po bid	3 years on treatment; post-colonoscopy/safety extension for additional 2 years without treatment; treatment stopped December 17, 2004	Determine the efficacy and safety of celecoxib vs. placebo in preventing the occurrence of newly detected colorectal adenomas in subjects at increased risk for colorectal carcinoma; evaluate biomarkers; establish safety
Prevention of Spontaneous Adenomatous Polyps (PreSAP) Trial	Pfizer	Levin and Arber	Double-blind, randomized, aspirin and country stratified, multi-center, international adenoma patients	1500	400, placebo po qd	3 years on treatment; post-colonoscopy/safety extension for additional 2 years without treatment; treatment stopped December 17, 2004	Determine the efficacy and safety of celecoxib versus placebo in preventing the occurrence of newly detected colorectal adenomas in subjects at increased risk for colorectal carcinoma; evaluate biomarkers; establish safety
Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT)	NIA	Breitner	Double-blind, randomized, multi-center, age (70 and over based on treatment arm) and site stratified subjects at risk of Alzheimer's (AD)	2625	1:1:1.5 ratio, 200 mg po bid celecoxib, 220 mg po bid naproxen, placebo	3 years treatment, 7 years follow-up; treatment stopped December 17, 2004	Evaluate efficacy of naproxen vs placebo and celecoxib in prevention of AD; establish safety
Celecoxib and/or Selenium in Treating Patients with Adenomatous Colorectal Polyps (SelCel) Trial	NCI	Lance, Alberts	Double-blinded, randomized, low-dose aspirin (81 mg qd) stratified, multi-center adenoma patients	1600	1:1:1:1 (400 subjects/arm) 400 mg po qd celecoxib, 200 µg/day selenium (SelenoExcell, selenium-enriched baker's yeast), placebo	3 to 5 years treatment; long-term (5 years) annual follow up via questionnaires. All celecoxib arm treatment was unblinded and stopped on December 23, 2004; selenium arm is	Measure the effects of treatment with a combination of celecoxib and selenium for three to five years on the recurrence of colorectal adenomatous polyps

Table 1. List of Celecoxib Studies under CTSA Project

Study	Sponsor	PI	Design/Cohort	Size	Dose	Duration	Objectives
						continuing	in relation to histologic type, number, size, and location than either agent alone; biomarkers, establish compliance and safety
5. Exemestane Compared with Anastrozole, with or without Celecoxib, in Treating Postmenopausal Women after Surgery for Primary Breast Cancer (MA27 Breast Adjuvant Trial)	NCI-Canada/ NCI Cooperative Groups	Goss	Double-blind, randomized, multi-center, stratified (lymph node, adjuvant therapy, aspirin) post-menopausal women with histologically or cytologically confirmed, receptor-positive, adequately excised, primary breast cancer.	6830	1:1:1:1, 2.5 mg/day exemestane, 1 mg/day anastrozole, with or without celecoxib (200 mg, two capsules twice daily—400 mg po bid)	5 years; celecoxib treatment for only 3 of the 5 years. Celecoxib treatment stopped 12/17/2004, other arms continued in blinded fashion)	Compare event-free survival between women treated with exemestane or anastrozole as adjuvant therapy and to determine the effect of adding celecoxib to those therapies.
Treatment of Diabetic Macular Edema Trial (NEI, 03-EI-0065)	NEI	Martin, Haller, Aiello, Ip	2x2 factorial design, double-blind, randomized; participants have diabetic retinopathy and clinically significant macular edema	100	200 mg po bid, placebo (50 per arm)	3 years; all subjects stopped treatment December 22, 2004; all subjects followed to December 2005	Compare (1) diode (micropulse) laser photocoagulation to mild Early Treatment Diabetic Retinopathy Study (ETDRS)-style focal photocoagulation and (2) celecoxib to placebo for three months prior to and following laser coagulation

As shown in the Table above, the designs of the studies under CTSA investigation were quite different from each other, and were at various stages of progress at the time of the CTSA analysis. They represented various cohorts and demographics, treatment periods and dosing, endpoints, and criteria for safety reporting. Therefore, to accomplish the task of a ‘pooled safety data analysis’ and an attempt to find answers to Question #1 (‘How are CCV safety data collected, categorized and analyzed within selected studies conducted across the NIH?’) and to Question #2 (‘How might CCV safety data be harmonized across NIH-sponsored trials, thereby facilitating the potential for data sharing?’), under this project, a standardized approach was developed. This was the first challenge.

The first step in this approach was to develop Manuals of Operations (MOPs) which clearly defined the scope of the project and provided details pertaining to the processes for standardization and harmonization of data as well as document collection, data distribution, database development, event adjudication, and data analysis. The two MOPs developed by CEC and CCSA are included in Appendices D and E. More details on the variations in the study designs and criteria for safety data collection and reporting are presented in the CTSA Statistical Plan (Appendix F).

The standardization/harmonization approach was based on development of common data elements (CDEs) across studies requiring design of a method for defining each required data element for CTSA analysis. For example, defining what is meant by ‘subject ID’ or ‘drug stop date’ or ‘off-study date’ and requesting these data elements to be pulled from each of the six study databases, regardless of the individual study data field names but, maintaining the definition of the data element per protocol. To accomplish this task, as stated in both MOPs, a series of templates (MS Word or MS Excel files) were developed. These include the CTSA Adverse Event Checklist (8/1/2005) in MS Word and the SAE Listing (6/15/2005) Excel file. An example of the Checklist for the NEI study is presented in Exhibit 1, below. The purpose of this checklist was to obtain general, higher level information for each study, to assist in selection of the reported events for adjudication. The second MS Excel template was used in an attempt to ‘harmonize’ the data for the pulled analysis. Therefore, each study reported the following data points for each randomized subject to a common cut-off date of January 29, 2005, (approximately six weeks post December 17, 2004, treatment termination date, allowing sufficient time for reporting any adverse events experienced as a result of treatment):

1. Patient ID Number
2. Study ID Number
3. Unique Event ID Number
4. Date of Randomization
5. Site Reported Event Onset Date
6. Site Reported Event Resolution Date
7. Site-Reported Event/Event Description
8. Site-Reported Narrative (*i.e.*, as completed on a study’s reporting form)
9. Study Reported Investigator Term
10. Study Reported Event Outcome
11. Study Reported Event Severity
12. Study-Reported Event/Event Description
13. Study-Reported Narrative (*i.e.*, as completed on a study’s reporting form)
14. Comments

Once the data were collected using the Excel spreadsheet, the events for adjudication were selected by the adjudication team as detailed in the CEC MOP, Appendix D. Upon completion of this task and as presented in CCSA’s MOP, source documentation were collected and forwarded to CEC for final adjudication and completion of the Adjudication Forms for CTSA Database entry. Once this task was completed and following quality control of the database data, it was forwarded to SCI for the final statistical analysis. Additional details pertaining to the study timeline for collection and database entry are provided under section IV. CCSA Project Tasks, below.

The second challenge was to meet the project timeline, as presented in Appendix C. As stated in the CCSA MOP, data and case documents were collected and forwarded to CEC from three studies (NEI, Selenium, and MA27; APC and Pre-SAP study data and case documentation had been collected previously based on the initial adjudication effort by CEC; therefore, there was no need for additional data collection and review). The ADAPT study data and case documentation were initially collected by CEC and copies were then provided to CCSA for central project filing. This deviation from the project procedures was requested by the ADAPT team and followed by both CEC and CCSA upon approval from NCI. Due to this deviation as well as the additional time for data and case documentation collection from each site, the project timeline was revised requiring the need for an additional nine months in collecting and processing the necessary documentation for this study. The review and inclusion of case data from this study was critical for the CTSA analysis, as the majority of the data for this analysis were provided by this study. Exhibit 2 below provides the number of case data reviewed and adjudicated from each four study. In total, 499 events were selected and adjudicated for this analysis.

The final challenge was to devise a plan for sharing and exchanging of the confidential research data amongst the team members, since the studies under the CTSA analysis were ongoing (some still being blinded) and the final data (including unblinded treatment information) had not been published. These were accomplished by enacting data sharing and confidentiality agreements among the team members, as well as specific non-disclosure agreements with CCSA, CEC and SCI. Additionally, the project met HIPAA requirements by maintaining subject identification confidential. For all data listings, only subject randomization numbers in addition to uniquely assigned event IDs were used. As part of the MOPs and per instructions to the CTSA study team members, all subject identifiers were masked from source and case documentation prior to arrival to CEC or CCSA for processing. All case data were filed and stored by CCSA using the uniquely assigned event IDs.

Exhibit 1. CTSA Adverse Event Checklist (8/1/2005)

Please email or forward this checklist along with the required documents to:

Email: dbagheri@ccsainc.com

Mailing Address:

Donya Bagheri, MS, DABT
Senior Director, Research and Development
CCS Associates, Inc.
2005 Landings Dr.
Mountain View, CA 94043

Please call if you have any questions: (650) 691-4400 x116 (office); (408) 221-8021 (Cell)

Thank you in advance for your contributions to this project.

Study	03-EI-0065 - Preliminary Multi-Center Assessment of Laser and Medical Treatment of Diabetic Macular Edema (CDME1)
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Please submit copies of the documents marked with an asterisk (*)	
Number of AEs collected to date	188 AEs from 70 patients by Jan 31, 2005
Were SAE data captured for this study? If so, was a study-specific SAE form or MedWatch or another form used?*	Yes. There was a study-specific AE form used to collect all AE data. A MedWatch was submitted by the site in cases of SAE. A blank copy of our study form set was sent to Ms. Bagheri on 6/29/05.
Are SAE reporting guideline and criteria available? Include SAE reporting time frame and criteria (<i>e.g.</i> , only drug-related events meeting the criteria were categorized as SAEs) to the sponsor, attribution and grading system	Summary of AE reporting procedures from the Manual of Procedures for this protocol is attached.
Were SAEs collected on hard copy forms or electronic forms?*	Electronic data forms, with MedWatch forms faxed into the Data Coordinating Center (DCC).
Are SAE data (including case data and hospital records) available in hard copy or electronically? Please specify.	Hard Copy
Was each SAE assigned a unique ID? If yes, what is the format (<i>e.g.</i> , numeric, alphanumeric, <i>etc.</i>)	No
Number of SAEs collected to date	14 SAEs from 12 patients by Jan 31, 2005

Was CTC used to code and grade SAE data? Is so, what version was used (e.g., 2.0 or 3.0)?	No
Number of events with CTC severity grade equal to or greater than 3	N/A
Were SAE data coded in any other way? If so, please include version and date of the dictionary (e.g., COSTART, MedDRA, other; please specify)	MedDRA version 8.0
Additional comments:	

Exhibit 2. Total Events Adjudicated per Study

Study	Events Received by CEC	Total Events Adjudicated
CelSel	67	68 (67 + 1 CEC Identified)
MA27	40	40
NEI	9	9
ADAPT	351	382 (351 + 31 CEC Identified)
TOTAL	467	499

IV. CCSA Project Tasks

This section describes in detail the tasks carried out by CCSA including timeframes for data collection, distribution, and adjudication. The accomplishments under each task were reported to NCI and SAIC on a monthly basis as part of the contract deliverables.

Task 1: Facilitate communication among the trial representatives and the NCI-NIH.

- 1. Arrange bi-monthly teleconferences.** Commencing in May 2005 through September 2007, teleconferences were organized and conducted with the CTSA Project Team, Working Group, and the Expert Panel. These calls were initially set-up as bi-weekly and subsequently moved to monthly, quarterly, and as on needed based schedule.
- 2. Generate and disseminate telecon/meeting agendas and minutes.** Agendas and minutes were prepared and distributed to the participants in advance of the teleconferences or within two weeks following completion of the teleconferences.
- 3. Generate and maintain roster of cross-trials safety analysis (CTSA) investigator and NCI/NIH staff contact information.** A contact list including phone and email addresses for the CTSA project team has been created and being maintained by Ms. Bagheri. Overall, the team had 52 members representing NCI, SAIC, CCSA, BWH/CEC, SCI, and representatives from APC, Pre-SAP, ADAPT, MA27, NEI, and Selenium (formerly SelCel) studies.

Task 2: Collect and facilitate data transfer between trials relating to:

1. CV safety data collection.

2. CV Safety data categorization. Based on the established format (templates, as described above), data listings for NEI (14 data records), MA27 (103 data records), and Selenium (166 data records) studies were received and processed. Data for the Pre-SAP and APC studies were collected prior to the start of this project and no additional listings were collected. The adjudication committee (Dr. Finn) reviewed the data listings for the MA27, NEI, and Selenium studies and selected 30, nine, and 66 cases, respectively, for collection. Case data including SAE/safety forms, Medical Monitor notes and assessment as well as other documentation such as hospital discharge information have been collected for the 30 MA27 cases, 9 NEI cases, and 66 Selenium cases. These were forwarded to BWH/CEC on October 5, 2005 (MA27 and NEI studies), October 21, 2005, February 6, 2006, and April 10, 2006 (Selenium study) for review. CEC queries were received for the Selenium study; these 14 queries were processed, case documentation collected and forwarded to BWH on February 7, 2006. Queries from review of the MA27 case documentation were received and processed on February 7, 2006; additional case documentation for these queries were received on April 10 and forwarded to BWH on April 11, 2006. Based on review of case documentation for these three studies, no additional queries were issued.

The initial data listings for the ADAPT study were received on 3/2/2006 and 3/23/2006 by CCSA and BWH/CEC; these listings were reviewed by Dr. Finn and case documentation were requested for 36 fatal events on March 27, 2006. Additional event descriptions were requested for 163 non-fatal events on April 5, 2006 by BWH. With assistance from Ms. Mercier, on May 9, 2006, the ADAPT staff (Ms. Piantadosi) had distributed memos containing 'study checklists' to the six ADAPT sites requesting additional information including case documentation for the 36 safety alerts. All data were received and processed; there were a total of 499 case documentations for CTSA analysis. All documentation was organized and stored in the project file.

Dr. Rosenstein (Pfizer) also provided a list of celecoxib studies to the team on 1/27/06; as discussed during the 2/8/2006 call; none of the studies met the CTSA criteria established at the 7/20/05 meeting. These criteria included: 'placebo-controlled, at least two years of treatment, celecoxib at any dose'. Therefore, the CTSA analysis was conducted based on safety data from these six studies.

CTSA Database. CCSA also finalized the structure of the CTSA Database based on discussions with SCI, NCI, and BWH in 2006. The database was tested and reviewed by SCI using case data from five 'dummy' adjudication forms data; the first batch of 71 completed adjudication forms was received on September 13, 2006 from CEC. CCSA Data Management finished data entry of these data on September 21, 2006 and generated a few queries for CEC review and resolution. The test CTSA Database was transferred to the SCI group on 9/29/2006. The second and third batches of the adjudications forms containing information from 216 cases were received on October 24, 2006; additional electronic notes were provided on November 10, 2006. The CTSA Database containing these data was transferred to SCI on November 7, 2006. The fourth shipment was received November 21, 2006, containing 40 additional adjudications forms; additional notes were provided on December 12, 2006. A CTSA Database transfer was made to SCI on December 15, 2006. Two additional shipments (5 and 6) were received on February 13 and 20th, 2007, respectively. Electronic notes associated with these shipments were received on February 21st and 27th, 2007; all data were entered into the CTSA Database within a week and quality controlled. A CTSA Database transfer was made to SCI on March 2, 2007 and the final transfer of the CTSA Database containing 499 data records was made to SCI on March 21, 2007.

Individual Study Reports. The SCI-prepared baseline data for each study was re-formatted and distributed by Ms. Bagheri to each CTSA study team member on May 4, 2007. These data tables were reviewed by each study team for accuracy and suggestions for modifications were communicated to SCI by May 18, 2007. In preparation for review of study specific reports, emails to each of the CTSA Team member for the six studies notifying them of the availability of this report and the requirement for the review process were sent by Ms. Bagheri on June 13, 2007. Individual study reports were distributed to previously identified CTSA Project Team member on July 13, 2007; questions and comments received from the study teams, except for ADAPT study, were collected by Ms.

Bagheri and forwarded to the Working Group for discussion, as necessary. On August 24, the ADAPT study team requested the datasets from SCI to duplicate the analysis as part of their review of the study report. Based on communications received by Dr. Viner on September 5, 2007, the ADAPT team also provided their approval of the study report.

CTSA Expert Panel. An introductory conference call with the Expert Panel (Drs. Greenhouse, Olkin, and Califf) was conducted on January 19th; minutes from this call were prepared by Ms. Bagheri. Copies of draft CEC MOP dated 1/23/06 and the draft Statistical Plan dated 1/19/06 were provided to the Expert Panel for review on 1/24/2006 and discussed during a call held on February 28, 2006; Ms. Bagheri prepared minutes and distributed it to the call participants on March 7, 2006. Based on the Expert Panel and CTSA team discussions, a draft final copy of the MOP was developed. Additionally, Dr. Wittes provided an updated Statistical Plan on July 13, 2006, for review by the Expert plan and the CTSA working group. An Expert Panel call was held on August 29, 2006, and updated Statistical Plan was discussed. Minutes from this call were prepared on August 30, 2006 for review and distributed to the group following approval from NCI. On December 13, 2006, the draft final copy of the Statistical Plan dated December 5, 2006, was distributed to the Project Team; the final version was distributed on 1/8/07 and an updated version with minor revisions dated April 10, 2007, was distributed to the CTSA Team on April 18, 2007. A copy of the final Statistical Plan is presented in Appendix F.

3. DSMB policies for each trial. All clinical trials conducted under an IND or IDE, such as those included in the CTSA analysis, are subject to regulatory (US or international) safety reporting requirements. For trials conducted under an IND in United States, these requirements include prompt reporting to FDA of certain serious and unexpected adverse events (see 21 CFR 312.32(c), 21 CFR 312.52, 21 CFR 812.46(b), 21 CFR 812.150(b)(1)). To ensure proper collection, review, and analysis of the safety data, sponsors may elect to establish an independent study DSMB to assist in achieving this objective. It should be noted that the DSMBs may provide support in other areas of investigational studies as stated in the FDA Guidance entitled “Clinical Trials Sponsors – Establishments and Operation of Clinical Trial Data Monitoring Committee”, dated March 2006. This guidance finalizes the draft guidance entitled "Guidance for Clinical Trial Sponsors: On the Establishment and Operation of Clinical Trial Data Monitoring Committees" dated November 2001.

The six studies under CTSA analysis all had DSMBs established with the primary function of safety monitoring. The collection of the DSMB policies was completed in latter part of 2005, and the following documents were collected: APC DSMB Charter 1/29/01; Pre-SAP: DSMB Charter 11/2/01; MA27 NCI Canada: 10/4/01; NEI DSMC: 02/08/2005; ADAPT DSM Policy: 11/20/02; updated Selenium study DSMB Plan based on the 12/2/2005 meeting. These are presented in Appendix G.

Based on review of these documents, the Exhibit below summarizes the compliance of the six studies to the March 2006 FDA Guidance regarding DSMB establishment and operation. As applicable, for studies sponsored by NCI (APC, Selenium; MA27 co-sponsored by NCI and NCI Canada), their compliance with the NCI guidelines entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials” approved by the NCI Executive Committee on June 22, 1999” are also summarized.

Exhibit 3: Summary of FDA/NCI DSMB Guidance Compliance and Studies under CTSA Analysis

FDA/NCI Guidance Criteria	APC	Pre-SAP	ADAPT	MA-27	NEI	Selenium
Committee Composition (Disclosure of Conflict of Interest/Financial Disclosure, Adequate Expertise)	√	√	√	√ ¹	√	√ ²
Charter Establishment (Meeting Schedule/Format, Interim Reports, Unblinding)	√	√	√	√	√	√
Confidentiality of Interim Data and Analyses	√	√	√	√ ¹	√	√ ²
Interim Reports Delivery	√	√	√	√	√	√
Defined Responsibilities: Interim Monitoring (for Effectiveness, for Safety, for Study Conduct, Making Recommendations to Sponsor/Steering Committee/IRBs)	√	√	√	√	√	√
Maintaining Meeting Records (Semi-Annual/Annual Teleconferences/Meetings)	√	√	√	√ ¹	√	√

¹MA 27 is co-sponsored by NCI and NCI Canada. The study DSMB Plan was modeled to fulfill the NCI Cooperative Group Data Monitoring Committee requirements. It did not specifically include a description of the conflict of interest and/or financial disclosure as well as assuring confidentiality of the interim data/reports. Format and maintenance of DSMB meeting/teleconference records were not well-defined.

²Selenium Study DSMB Plan did not specifically include a description of the conflict of interest and/or financial disclosure as well as assuring confidentiality of the interim data/reports. It should be noted that this study used the Colon Cancer Prevention Program Project (CCPPP) External Data and Safety Monitoring Committee (EDSMC) as well as the CCPPP formal Internal Data and Safety Monitoring Committee (IDSMC). The IDSMC assists with monitoring of adverse events in preparation of reports for EDSMC meetings. The EDSMC meets at least twice a year to review the study interim reports.

Based on review of the data summarized in the Exhibit above, it is noted that all sponsored studies (NIH, NCI Canada, or private industry), have adhered mostly to the NCI and/or FDA DSMB establishment and operation guidance. A few deficiencies in disclosing conflict of interest and/or maintenance of data confidentiality were noted for the Selenium and MA27 studies; however, both studies appear to have met their governing safety monitoring committees and therefore the specific references to these requirements in the specific study DSMB plans could have omitted.

4. Data sharing policies across trials and the NIH. Data sharing and confidentiality agreements were drafted and distributed to the team during the July 20, 2005, face-to-face meeting; these are presented in Appendix H. During this meeting, the various authorship models were also provided for group discussion; these are summarized in the meeting minutes presented in Appendix A. On March 15, 2006, a specific teleconference was held to discuss the authorship model for the manuscripts developed under this project. Following a group

discussion, all CTSA team representatives, except for the ADAPT team who preferred Option 1: 'Writing committee/CTSA study group listed as authors', voted for Option 4: 'Individual authors from each study listed on the manuscript'. This approach entails having the names of all the main contributors (*e.g.*, investigators from each study, CTSA adjudication committee and statisticians) listed as authors followed by representatives from each trial including the 'hands-on' individuals. It was noted that since most journals no longer have a limitation on the author list, this approach would work. It was agreed by the group that names of two representatives from each study be listed as authors. A suggestion was made to ask the principal investigator from each trial to name individuals who contributed heavily to CTSA, to ensure that CTSA "heavy lifters" -- who otherwise might not have come to the attention of CTSA organizers - might be considered for authorship. This information has been collected; the manuscript preparation by SCI and CEC team is under way.

Task 3: Assist NCI staff in compiling, analyzing, drafting, and editing CTSA-related manuscripts, evaluation of documents, and summary reports.

Technical and editorial support has been provided to NCI for activities described under Tasks 1 and 2, above. This effort has continued throughout the project including preparation of the manuscript by the SCI and CEC team.

V. Findings

Overall, the CTSA project proved to be a successful collaborative effort meeting its goals. The project Working Group (NCI, CEC, SCI, and CCSA) worked effectively and efficiently together and met the two-year project timeline. However, the initial six-month project timeline could not be met due to difficulties in collecting data listings and case documentation for one of the studies under CTSA analysis. This impacted the overall project timeline by an additional nine months.

The main objective of the CTSA analysis was to address the following 3 questions and from the results of the meta analysis provide information to potentially identify appropriate changes to NIH clinical trial review and data management:

Question #1: How are CCV safety data collected, categorized, and analyzed within selected studies conducted across the NIH?

Question #2: How might CCV safety data be harmonized across NIH-sponsored trials, thereby facilitating the potential for data sharing?

Question #3: How might real-time data sharing be achieved (*e.g.*, between Data and Safety Monitoring Boards, DSMBs) in order to protect patient safety in ongoing trials? Within an institute? Across institutes?

As indicated above and illustrated in Table 1, the designs of the studies under CTSA investigation were quite different from each other and were at various stages of progress at the time of the CTSA analysis. They represented various cohorts and demographics, treatment period and dosing, endpoints and criteria for safety reporting as described in details in the CTSA Statistical Analysis Plan. Therefore, in order to find answers to questions 1 and 2, above, MOPs which clearly defined the scope of the project and provided details pertaining to the processes for standardization and harmonization of data as well as document collection, data distribution, database development, event adjudication, and data analysis were developed by CEC and CCSA.

The standardization/harmonization approach was based on development of CDEs across studies requiring design of a method for defining each required data element for CTSA analysis. As a result, a series of templates were designed for collection of the desired information for adjudication. This effort is very similar to that of the Cancer Biomedical Informatics Grid (CaBIG) work underway by NCI. The CaBIG has launched the initiative to accelerate research discoveries and improve patient outcomes by linking researchers, physicians, and patients throughout the cancer community. CaBIG is the cornerstone of NCI's biomedical

informatics efforts to work together, leveraging valuable resources to transform cancer research into a more collaborative, efficient, and effective endeavor. The Grid provides a variety of bioinformatics tools and capabilities that span the entire continuum of clinical research, pathology and genomics. Access to the current inventory of caBIG tools, infrastructure, and data resources developed by the community is available (see <https://cabig.nci.nih.gov/inventory/>).

In an attempt to find an answer to question 3, DSM plans were collected and reviewed for all six studies. Overall, the DSM plans met the FDA and/or NIH-requirements. But, none of the plans included provisions for ‘real-time’ access to data by DSMBs for safety or other analysis, as this is not currently an FDA or NIH requirement. However, with advances in technology and accessibility to secure and web-based electronic data management systems [*e.g.*, caBIG Tools, Remote Data Capture (RDC)] containing investigational safety data, such an objective may be achieved.

VI. References

1. Solomon SD, McMurray JJV, Pfeffer MA, *et al.* Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *New Engl J of Med* 2005; 352: 1071–1080.

Appendix 1: CTSA July 20, 2005 Face-to-Face Meeting Agenda and Participant List

**Cross Trials Safety Analysis (CTSA) Meeting
July 20, 2005 – Pook’s Hill Marriott**

8AM	Introductions (Hawk)
8:15	CTSA Premise & Goals (Hawk)
8:45	Data Sharing Agreement (NCI)
10:00	BREAK
10:15	Draft Protocol MOP (Solomon)
10:45	Statistical Plan: Review & Revision (Wittes)
12:00	WORKING LUNCH
1:00	Statistical Plan: Revision (Wittes)
2:00	CTSA Pooled Analysis: Defining Elements & Methods (Wittes)
3:00	CTSA Timeline, Q & A (Bagheri)
3:15	Summary of Action Items (Hawk)

CTSA Meeting

July 20, 2005

Meeting Attendees

NAME	STUDY	EMAIL	PHONE
ERNE HAWK		HAWKE@MAIL.NIH.GOV	301.594.2731
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Appendix 2: CTSA July 20, 2005 Meeting Minutes

Cross-Trial Safety Analysis (CTSA) Meeting
Wednesday, July 20, 2005
8:00 am–3:00 pm EDT
Pook's Hill Marriott

Attendees

NCI: E. Hawk, J. Viner, L. Whitney, L. Ford
BWH: S. Solomon, P. Finn
Statistics Collaborative: R. Fowler, J. Wittes
Pre-SAP: B. Levin
APC: M. Bertagnolli, A. Zauber
Pfizer: C. Eagle, R. Rostenstein (on phone)
ADAPT: B. Martin, B. Piantadosi, K. Meinert, S. Molchan
NEI: J. Kim, K. Selley
MA27/NCI Canada: J. Pater, J. Zujewski
SelCel: S. Obara
SAIC: J. Derge, D. Dougherty
CCSA: D. Bagheri, C. Sigman, L. Doody, D. Milgram, K. Guyton

Introductions (Hawk)

CTSA Premise & Goals (Hawk)

Dr. Hawk provided an overview of the CTSA project and thanked everyone for their participation. He continued by providing the background for the safety analyses performed for the APC and Pre-SAP studies. In October 2004, the APC DSMB recommended convening a special body to look at CV risk in the study following withdrawal of Vioxx from the market. An independent CV safety committee (blinded CEC: Drs. Solomon and Finn) and a second committee (unblinded CV Review Committee: Drs. Pfeffer, McMurray and Wittes) were established. The steps for the APC analysis included:

- a) while both committees remained blinded: preparation of a statistical analysis plan; data compilation, verification and adjudication
- b) while the CV review committee was unblinded: analysis; presentation to the DSMB; and
- c) while both committees were unblinded: publication.

A hierarchical risk analysis was performed using composite endpoints. For the APC study, a clear difference between active and placebo by a logrank test emerged as well as a monotone relationship between hazard ratio and dose. No evidence of differential hazard by baseline risk factors was found.

The Pre-SAP cohort is similar to the APC cohort, except it is primarily ex-US. Only one celecoxib dose (400 mg qd) was used in the study. Both trials have extension phases after stopping treatment. The APC and Pre-SAP analyses ended collection of SAEs one month after end of treatment. {Post-meeting note by Linda Doody: SAEs through 37 months after randomization for APC and Pre-SAP analyses }

The Pre-SAP cohort had 15% aspirin use (APC had 30%), and less use of lipid-lowering drugs (APC had 30%). The hazard ratio showed no statistically significant increase in CV events associated with celecoxib, and no evidence of differential hazard ratio based on baseline risk factors. A logrank test of CV risk showed no difference between arms.

The results of the APC analysis were published in the March 17, 2005 NEJM (on-line publication was February 17). As noted, in the APC study, the data showed a statistically significant increased risk of CV events associated

with celecoxib, but no such effect was observed in the Pre-SAP study. As a result of these analyses, the CTSA project was initiated to examine the effects of celecoxib in six studies (APC, Pre-SAP, SelCel, ADAPT, MA 27, NEI/Eye).

Dr. Meinert asked about the duration of safety data collection for the APC and Pre-SAP studies. Dr. Hawk explained that there are extensions to both of these studies, and the subjects in the extension studies will be followed until their year 5 colonoscopies. Dr. Wittes stated that for the APC and Pre-SAP analyses the data were collected to month 37 (or one month after stop of treatment for those who completed all 36 months of the original study).

The CTSA project is a collaboration of NCI and the six studies named above, with contributions from BWH, Statistics Collaborative, Inc. and CCSA. SAIC facilitates the necessary contracts for these organizations. The products of the project are:

1. Manual of Operations (MOP)
2. Statistical plan
3. Adjudicated event listing from each trial
4. CTSA CV risk meta-analysis (or pooled analysis) as a peer reviewed publication
5. CTSA evaluation of cross-institute policies and procedures related to these celecoxib clinical trials.

Dr. Meinert asked about the sponsors for each study. They are as noted below:

1. APC is an NCI, DCP-sponsored study.
2. Pre-SAP is sponsored by Pfizer.
3. SelCel trial is funded by NCI through a P01 held by the University of Arizona.
4. ADAPT trial is funded by NIH, NIA.
5. MA 27 trial is funded by NCI Canada and NCI.
6. NEI trial is an investigator-initiated study (Dr. Chew) with funding from Pfizer.

Data Sharing Agreement (NCI)

The group received copies of the draft CTSA Statement of Intent and the Confidential Disclosure Agreement for review and discussion.

CTSA Statement of Intent:

This document has several sections which were briefly described by Dr. Hawk:

- A. CTSA Background and Rationale
- B. CTSA Collaborators
- C. Collaborator Roles
- D. CTSA Decision-Making Bodies/Process: Dr. Hawk emphasized that the project covers analysis of only

the adjudicated data based on the collected data for each study.

- E. Publications/Presentations
- F. Authorship Options

Dr. Whitney stated that the goal of this document is to agree on the intent, objectives and products of this project; this document is to be signed by each study Principal Investigator. The CTSA Confidentiality Agreement covers the legal issues related to data ownership and would be signed by a legal representative for each study.

Dr. Hawk asked for the group's input in terms of the approach and the mechanism for conducting this project; no other comments were provided by the group during the meeting.

The next topic covered was authorship on the main manuscript. Dr. Hawk noted that several other manuscripts are expected from this project. Dr. Meinert expressed concerns about the manuscript authorship, and specifically who will be listed by name as authors on the main manuscript. Dr. Hawk solicited input from each study's representative in this regard:

Drs. Bertagnolli and Levin felt that a group authorship would be appropriate. Dr. Meinert also favored this approach. Ms. Seeley and Ms. Obara deferred to their Principal Investigators; Ms. Seeley expressed that possibly Dr. Chew would favor group authorship and will check with her. Dr. Pater also expressed that he would need to check with other study investigators, but the group authorship approach seems reasonable.

Dr. Hawk stated that the primary names on the manuscript would be Drs. Solomon and Wittes because of their unique position on this project followed by names from the groups. Dr. Solomon and Wittes favored having a writing group who will be responsible for writing and reviewing the manuscript. Dr. Eagle also favored this mechanism, and recognizing other collaborators as contributors to the project.

Dr. Pater noted that the Statement of Intent document describes two groups: a writing group (authors for the manuscript) and the working group (all study collaborators).

As a result of the discussion, four options for manuscript authorship are under consideration; collaborators are asked to submit their choices by email to Drs. Viner and Hawk (Action Item):

1. Writing committee/CTSA study group listed as authors.
2. Scott Solomon and Janet Wittes listed as authors followed by acknowledgment of the study teams.
3. Scott Solomon and Janet Wittes listed as authors along with any other cardiologists and statisticians contributing to the writing effort for the meta analysis; these additional cardiologists and statisticians will be selected by Drs. Wittes and Solomon (**Action Item**).
4. Individual authors from each study listed on the manuscript.

Potential changes for the document/**Action Items**:

1. **Make the document specific for analysis of only CV events and not all events. Specifically page 2 under 3: Event Adjudication Center should perhaps be changed to Cardiovascular Event Adjudication Center.**
2. **Review of section F. Authorship Options (as well as the whole document) was requested by Dr. Hawk. Comments to be sent to him.**

Confidential Disclosure Agreement:

Several points were raised:

1. Is the confidentiality agreement needed? Dr. Whitney affirmed that each group can elect to sign or not sign the CTSA confidentiality agreement.
2. Dr. Hawk stated that this document would only cover the CV related events and changes in the document will be made to reflect this fact.
3. As pointed out by Mr. Dougherty, none of the CTSA project data is subject to FOI and therefore can remain confidential and not publicized other than through the planned publications.
4. Drs. Solomon and Wittes expressed that the adjudicated CV dataset, along with baseline data, is the only dataset that is reviewed/analyzed by these groups. Also, Dr. Solomon's group will adjudicate the data, but will not have the randomization data for their review; therefore, their analysis will be performed in a blinded fashion. Dr. Solomon also pointed out that the adjudicated data could be sent back to each study to be published, if desired, by each study group. Alternatively, as Dr. Meinert pointed out, each study could publish its results independently of the adjudicated data.

5. HIPAA compliance was raised as a concern in reviewing the data for analysis. It was noted that several data points (*i.e.*, subject initials, birth date, *etc.*) once combined could potentially result in HIPAA noncompliance. After some discussion, it was decided that, based on the proposed data set for collection, HIPAA is not an issue.

Draft Protocol MOP (Solomon)

Dr. Solomon described the process for adjudication and analysis work performed for APC and Pre-SAP. He expressed that a similar approach had been used for meta-analysis of other data including that from a 15,000 patient study reviewing cases for over 4000 deaths. For the APC and Pre-SAP studies, the data collection and analysis phases took place between October and December 2004 with the manuscripts published in March 2005; data were published online prior to the FDA meeting in February 2005.

The APC and Pre-SAP processes involved review of the initial SAE screening log (MS Excel format) to identify all potential CV-related events. For the APC study, over 600 events were reviewed and 212 were categorized as CV-related. Detailed source documentation was requested and reviewed. A review folder was prepared for each case. Each case folder was reviewed by Drs. Solomon and Finn. For classification of deaths, CV, non-CV and unknown categories were used. For the CV-related death category, several sub-categories were used to further classify specific fatal events (*e.g.*, pulmonary embolism, *etc.*). All non-fatal CV-related events (*e.g.*, MIs, stroke, revascularization, resuscitated sudden death, congestive heart failure) were also reviewed. An adjudication review form (ERF) was prepared for each case. There will be a new adjudication form for review by CTSA group.

The challenge for the CTSA project will be the differing data formats and the variety of data which have been collected for each study. Additionally, the studies were not designed specifically to collect CV-related events, The primary endpoint for each study was non-CV.

Dr. Meinert asked whether if in confining the safety data analysis to just CV-related events we were limiting ourselves too much. He asked whether we should be considering beneficial effects. Dr. Bertagnolli noted that the sole aim of the study is to cover the CV-related events associated with the study treatment arms including placebo. The risk-benefit analysis can only be made when the efficacy data are available.

Statistical Plan: Review & Revision (Wittes)

CTSA Pooled Analysis: Defining Elements & Methods (Wittes)

Dr. Wittes explained that the goal of her presentation is address issues regarding the statistical analysis for this project with the hope of making decisions.

Dr. Solomon covered the baseline variables collected for the APC and Pre-SAP analyses. These included: age, sex, history of CV disease, diabetes, aspirin use, and use of lipid lowering drugs. Other variables such as race/ethnicity, geographic region and alcohol use could be of interest for analysis under the CTSA project. For the APC and Pre-SAP analyses, other variables were not considered, but potentially could be valuable for the CTSA analysis.

The possible analyses include:

1. Cox model with treatment as only covariate.
2. Stratification by NSAID use: Dr. Wittes asked whether we should include the stratification randomization within each study for the CTSA project. She stated that although it was not done for the APC and Pre-SAP studies, she favored doing it in the meta-analysis. The consensus of the group was to preserve the randomization strata in the meta-analyses.

3. The group discussed whether each study would be considered a separate stratum for the meta analysis. Strong sentiment was expressed on both sides with Drs. Pater and Wittes most strongly favoring keeping each study as a stratum.
4. The group discussed how to handle censoring. For APC, a subject who stopped drug but remained on study was not censored. This is very different from the Vioxx study, in which subjects were followed on study only until drug was stopped plus 14 days.
5. The group discussed how to handle different follow-up times. In ADAPT, some subjects have been on study four years. Only APC, Pre-SAP and ADAPT could be used for a three-year analysis. For the APC and Pre-SAP studies, all safety data were collected for subjects receiving drug treatment as part of the 36-month study plus 30 days after stop of study drug treatment. The cut-off date for the APC and Pre-SAP analyses was January 6, 2005. The data cut-off date for the CTSA analysis will be 30 days past the drug treatment stop date. For the APC and Pre-SAP studies, since the data cut-off date was January 6, 2005, the database will be searched for additional SAEs occurring prior to this date and reported to NCI after January 17, 2005. This dataset will be provided for adjudication to BWH and Statistical Collaborative groups.

Other Endpoints-Hierarchical: Other endpoints (*e.g.*, CV death with the following, in hierarchical order: MI, stroke, HF, angina, need for CV procedure, other cardio/cerebrovascular event) were also included in the APC and Pre-SAP analyses.

Follow-up Time: For the other four studies (excluding APC and Pre-SAP), all events from time of randomization to planned end of study drug treatment (ADAPT and MA-27, December 17, 2004; SelCel, December 20, 2004; and NEI, December 22, 2004) or the date of loss to follow-up (does not include drop out or withdrawal of consent?) will be collected. The question of how many patients were lost to follow up on each study was raised; for the MA 27 and NEI studies, only one subject/study has been lost to follow-up. In the ADAPT and SelCel studies, approximately 100 subjects have been lost to follow-up. **Ms. Obara will check on this number for SelCel and get back to the group.**

Subgroups: The following subgroups were included in the analysis of the APC study: age (below or above 60), sex (male/female), baseline cardiovascular risk factor: yes/no (prior CV event or current smoker or diabetes or use of low-dose aspirin or use of lipid-lowering drugs), diabetes: yes/no, low-dose aspirin use: yes/no, lipid-lowering drug: yes/no. The group discussed whether to use these baseline subgroups as well as race/ethnicity or a cardiovascular risk score. The group did not decide what baseline variables to use. All agreed that for the factorial design studies (SelCel and MA27), the alternative treatments should constitute baseline subgroups for analysis.

Dr. Wittes suggested the following questions for the meta-analysis:

Do celecoxib and placebo differ?

Does dose matter?

Does regimen matter?

Does baseline risk matter?

Does risk emerge early or late?

Dr. Hawk added that the studies selected for the CTSA project, except for the NEI study, have over 500 subjects enrolled, with two years of treatment and are placebo-controlled. The NEI study was included because of the cohort (diabetics) and the number of SAEs that have been collected. Dr. Hawk asked the group whether more studies be included in this analysis and whether a minimum number of cardiovascular SAEs, for example 10, should be required. Several people commented that studies having no cardiovascular SAEs would not add any value to the analysis, as the “numerator” rather than the denominator is the contributing factor to the comparison of drug to placebo. Dr. Eagle pointed out that eliminating the studies with very few cardiovascular events would produce an overestimate of the absolute risk. Dr. Eagle questioned the duration of treatment (at least two years) being a criterion for selecting the studies for this analysis. **In order to identify possible additional studies for**

inclusion in the CTSA analysis, Dr. Eagle will provide a list of studies that satisfy the following criteria: placebo-controlled, at least two years of treatment, celecoxib at any dose.

CTSA Timeline, Q & A (Bagheri)

Ms. Bagheri provided the timeline for the CTSA project. The project timeline currently shows a starting date of May 2, 2005 with a publication expected by December 29, 2005; it is expected that this timeline will be changed to accommodate additional planning time needed or additional studies to be included. It was also noted that a template for SAE collection has been provided to the team, with the intent of collecting the SAE listings by July 30, 2005. The group discussed the value of collecting all AEs, since criteria for SAE reporting for each study are very different and the data set would be more complete if all AEs, rather than only SAEs, are provided for selection and adjudication. **Post meeting note: Per NCI's direction, all AEs instead of SAEs will be collected.** Additionally, other variables requested by Statistics Collaborative and BWH's will be collected. A teleconference during the week of July 25th will be held between NCI, CCSA, BWH, and Statistics Collaborative to better define these variables. The outcome of this call will be shared with the group. Dr. Meinert noted that approval of all the ADAPT investigators is required prior to any data transfer from the ADAPT trial; the investigators will meet on August 2, and so additional time beyond July 30 may be required. A new schedule for data collection based on this information will be set and communicated to the group.

Summary of Action Items (Hawk)

Dr. Hawk thanked the group for participating; the minutes from this meeting will be distributed to the whole project team. Action items from the meeting are summarized below.

				STATUS
7/20/2005	All		Review of the Confidentiality Disclosure Agreement; send comments to E. Hawk	In progress
7/20/2005	Study Principal Investigators		Email choice of authorship model to Dr. Hawk	In progress
7/20/2005	SAIC, BWH, Statistics Collaborative		Complete contracts.	In progress
7/20/2005	Solomon, Wittes		Select additional cardiologists and statisticians as contributors to the Writing Group for preparation of the manuscript	Will start after contract is signed.
7/20/2005	Obara		Lost to follow-up subjects, provide the total number	In progress
7/20/2005	Eagle		List of celecoxib trials based on the defined criteria	In progress
7/20/2005	CCSA, BWH, Statistics Collaborative		Teleconference to be held week of July 25 th to define additional required data elements for data analysis	In progress

Appendix 3: Revised CTSA Project Timeline

ID	Task Name	Duration	Start	0	2001		2002		2003		2004		2005		2006		2007		2008		2009		2010	
				Qtr 3	Qtr 2	Qtr 1	Qtr 4	Qtr 3	Qtr 2	Qtr 1	Qtr 4	Qtr 3	Qtr 2	Qtr 1	Qtr 4	Qtr 3	Qtr 2	Qtr 1	Qtr 4	Qtr 3	Qtr 2			
19	Design forms and reports	9 days	Wed 11/30/05																					
20	Train project team on data entry	2 days	Mon 12/5/05																					
21	Maintain system	214 days	Tue 11/22/05																					
22																								
23	Task 3 Data Collection, Entry, QC and	215 days	Mon																					
24	Data Collection	149 days	Mon 5/23/05																					
25	Communicate with main study sites; share study matrix requirements	1 day	Mon 5/23/05																					
26	Collect Study protocols, ICs, CRFs and DSMB documentation (charter)	11 days	Tue 5/24/05																					
27	Extract Protocol, ICs, and relevant CRF and DSMB charter data into study matrix Excel	15 days	Thu 7/21/05																					
28	Collect SAE Listings in MS Excel Format (Excludes ADAPT Listings)	28 days	Wed 8/24/05																					
29	Review SAE Listings (Excludes ADAPT Listings)	17 days	Mon 10/3/05																					
30	Organize SAE Listings (create case file folders per CEC MOP, Excludes ADAPT)	22 days	Wed 10/5/05																					
31	Query missing SAE information (Excludes ADAPT Listing)	21 days	Fri 10/7/05																					
32	Complete SAE case files (including review, QC and organization)	48 days	Wed 9/28/05																					
33	Prepare case files for shipment to BWH	45.2 days	Wed 10/5/05																					
34	Data Shipment to BWH/Review of Cases	118 days	Wed 10/5/05																					
35	Prepare shipment logs and ship the cases for CEC review	62 days	Wed 10/5/05																					
36	Receipt of cases and CEC Review	60 days	Fri 10/7/05																					

ID	Task Name	Duration	Start	0	2001		2002	2003		2004		2005		2006		2007		2008		2009		2010	
				Qtr 3	Qtr 2	Qtr 1	Qtr 4	Qtr 3	Qtr 2	Qtr 1	Qtr 4	Qtr 3	Qtr 2	Qtr 1	Qtr 4	Qtr 3	Qtr 2	Qtr 1	Qtr 4	Qtr 3	Qtr 2		
37	Address queries from CEC review	42 days	Thu 12/1/05																				
38	Re-review the cases and provide resolutions, as necessary	64 days	Tue 11/1/05																				
39	Complete Physician Review Forms	86 days	Mon 10/17/05																				
40	Submit Physician Review Forms to CCSA for data entry	53 days	Thu 12/1/05																				
41	Enter Physician Review Forms into MS Access Database	51 days	Mon 12/5/05																				
42	QC entered physician review data (10% of entered data)	12 days	Tue 2/14/06																				
43	Provide preliminary database transfer to CEC for review	1 day	Mon 3/6/06																				
44	Review database and request any other changes; freeze database for analysis	4 days	Tue 3/7/06																				
45	Prepare data listings from the freedzed database for statistical analysis; CEC to	5 days	Mon 3/13/06																				
46	Task 4 Data Analysis by CEC	207 days	Thu 12/1/05																				
47	Review SAE listings and reports for analysis	7 days	Mon 3/20/06																				
48	Request additional SAE information or listings, if necessary	5 days	Wed 3/29/06																				
49	Obtain additional requested SAE information or listings	6 days	Wed 4/5/06																				
50	Obtain baseline and randomization data by Statistical Collaborative for analysis	72 days	Thu 12/1/05																				
51	Finalize data listings for analysis	5 days	Mon 4/17/06																				
52	Perform statistical analysis of the data (version 0), distribute for review	46 days	Fri 4/21/06																				
53	Revise statistical analysis of the data (version 1) after review and receipt of comments from	11 days	Fri 6/23/06																				
54	Revise statistical analysis of the data (version 2) after review and receipt of comments from	11 days	Fri 7/7/06																				

ID	Task Name	Duration	Start	0	2001		2002	2003		2004		2005		2006		2007		2008		2009		2010	
				Qtr 3	Qtr 2	Qtr 1	Qtr 4	Qtr 3	Qtr 2	Qtr 1	Qtr 4	Qtr 3	Qtr 2	Qtr 1	Qtr 4	Qtr 3	Qtr 2	Qtr 1	Qtr 4	Qtr 3	Qtr 2		
55	Revise statistical analysis of the data (version 3) after review and receipt of comments from	11 days	Fri 7/21/06																				
56	Prepare draft of the manuscript	75 days	Mon 4/24/06																				
57	Review draft manuscript	13 days	Mon 8/7/06																				
58	Finalize manuscript	18 days	Wed 8/23/06																				
59	Task 5 Project Report	205 days	Mon 12/5/05																				
60	Draft format for report; include format for DSMB charter/DSMB plan data presentation	7 days	Mon 12/5/05																				
61	Distribute the report format for review; receive comments and implement for	18 days	Wed 12/14/05																				
62	Prepare preliminary report based on available data (background, rationale, study	15 days	Mon 1/9/06																				
63	Prepare a draft after results of the Statistical analysis and manuscript are	72 days	Mon 4/24/06																				
64	Review draft of the report	15 days	Wed 8/2/06																				
65	Revise the report, as necessary	7 days	Tue 8/22/06																				
66	Finalize report	11 days	Fri 9/1/06																				



Cross Trials Safety Analysis (CTSA) Celecoxib Project

Clinical Endpoint Committee Manual of Operations

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I. Introduction

The Clinical Endpoint Committee (CEC) for the Cross Trials Safety Analysis (CTSA) project* will be responsible for providing a clinical review and adjudication of all reported deaths and other reported events** determined to be of a cardiovascular nature. The purpose of this review and adjudication is to classify all events received by the CEC into Cardiovascular or Non-Cardiovascular categories. Please refer to the Statistical Analysis Plan under separate cover that provides more in depth explanation of the CTSA project, its studies and the statistical analyses that this project will endeavor to perform.

The primary objective of the CEC is to review and classify, or adjudicate, all reported events in a consistent and unbiased manner, in a blinded fashion without regard for which study the patient is participating in or a subject's treatment assignment. Specifically, the primary objective of the CEC in the CTSA trial is the further categorize Cardiovascular and Non-Cardiovascular events into appropriate sub-categories. Since this is a retrospective review and classification, the CEC will base its adjudication of these events on its clinical expertise and judgment, using widely accepted criteria of such events. See Appendix A for the criteria used in classifying each event.

** The CTSA project was formed when the CEC's results from the APC and Pre-SAP trials were released. It was determined that further analysis of cardiovascular risks associated with taking celecoxib was needed. Please refer to the individual protocol of each of the above trials for more information related to each trial. Studies included in the CTSA project are as follows:*

1. Adenoma Prevention with Celecoxib (APC) Trial
2. Prevention of Spontaneous Adenomatous Polyps (PreSAP) Trial
3. Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT)
4. Celecoxib and/or Selenium in Treating Patients With Adenomatous Colorectal Polyps (SelCel) Trial
5. Exemestane Compared With Anastrozole, With or Without Celecoxib, in Treating Postmenopausal Women After Surgery for Primary Breast Cancer (MA27 Breast Adjuvant) Trial
6. Treatment of Diabetic Macular Edema Trial (03-EI-0065)

*** NOTE: Attention will be paid throughout this document to refer to the material that is received by the CEC as simply 'events' and not as SAEs or endpoints since a) not all events received by the CEC will be reported as an SAE in a given study, and b) since this is a retrospective review, events received by the CEC may not be reported as an endpoint in a given study. For purposes of this document, 'events' will refer to all deaths and other non-fatal cardiovascular events.*

II. Roles and Responsibilities

A. Clinical Endpoint Committee

The CEC is based out of Brigham and Women's Hospital Clinical Endpoint Center and is comprised of the CEC Chairman, a Physician Reviewer and administrative project staff. All members of the CEC are centrally located at Brigham and Women's Hospital which allows for close, consistent collaboration on this project. The CEC was responsible for providing event review and adjudication services for the APC and Pre-SAP trials; therefore, it was logical for the same group to be responsible for providing the same services to other trials using Celebrex.

Scott D. Solomon, MD, the Clinical Endpoint Center's Co-Director, will serve as both CEC Chairman and final adjudicator (Co-Reviewer). Dr. Solomon is responsible for:

4. providing overall leadership,
5. providing review of all events received,
6. ensuring events are reviewed in a consistent and unbiased manner throughout the period of work for all studies and that the data produced is of a high-quality and free from errors,
7. overseeing work completed by other members of CEC and that all work is performed in accordance with established internal SOPs.

Peter V. Finn, MD, the Center's Clinical Project Manager, will serve as the primary Physician Reviewer. Dr. Finn is responsible for:

8. pre-reviewing all Event Screening Logs (See Section V.A.) to determine which events should be sent to the CEC for review and adjudication,
9. providing primary review of all events received,
10. generating queries for additional information, as appropriate,
11. ensuring that all events are presented to and reviewed by Dr. Solomon,
12. providing clear and thorough documentation regarding the rationale for adjudication and any pertinent issues or discussions with Dr. Solomon,
13. completing and signing the final adjudication forms.

Renée Y. Mercier, the Center's Administrative Director, will serve as the Project Manager. Ms. Mercier is responsible for:

14. establishing a tracking database,
15. ensuring the proper internal distribution and retrieval of all events, queries and query responses,
16. providing quality assurance monitoring of every final adjudication form as well as appropriate documentation by Physician staff,
17. serving as the primary liaison with study leadership,
18. overseeing all day-to-day operational aspects of the CEC in accordance with established internal SOPs,
19. invoicing of all monies due per contract.

Chau M. Duong will serve as the Project Coordinator and will assist the Project Manager in the day-to-day operations of the CEC in the tasks described above.

B. Science Applications International (SAIC) & National Cancer Institute (NCI)

SAIC will work as a government agent directly for the NCI, which directly sponsors the studies involved in this project. SAIC will be responsible for administering the subcontract between SAIC and the BWH CEC.

C. CCS Associâtes, Inc. (CCSA)

Relevant to this MOP, CCSA will provide the following:

1. Create templates for collection of the required events and study data for analysis.
2. Collect the events based on the required data points.
3. Collect additional study data based on the required data points for analysis.
4. Collect the supporting event documents (e.g., case data information such as hospital discharge records).
5. Organize and maintain the project files and the collected data from the studies.
6. Prepare and submit the Event Screening Logs, Event Shipment Logs, and Adjudication Shipment Logs to CEC.
7. Prepare the manila-labeled case folders, organize the required documents and ship to CEC.
8. Communicate with the study sites ; process CCSA and CEC queries, as necessary.

9. Maintain tracking log files for the Event Screening Logs, Event Shipment Logs, and Adjudication Shipment Logs as well as the manila case folders.
10. Develop and maintain a shadow file of the manila-labeled case folders at CCSA.
11. Receive and process the Final Adjudication Forms.
12. Enter the Adjudication Forms data into the MS Access Database.
13. QC the entered data in MS Access Database.
14. Prepare data sets from the MS Access Database and send to Stats Collaborative for analysis.
15. Store project documents, files, and electronic data.

D. Statistics Collaborative (SCI)

SCI, which will serve as the statistical center for the CTSA, will have primary responsibility for analysis of the data on the cardiovascular safety for each of the six clinical trials to be included in this analysis. To that end, it will draft a data analysis plan to describe the planned statistical analyses for each trial and for the pooled analysis of all five trials. The pooled analysis will be based on individual patient data. Only after the CTSA Steering Committee has agreed upon the plan will SCI receive data from the trials.

Each trial will send SCI baseline and follow-up data as agreed upon above as well as its randomization list. The CEC will send SCI a database or spreadsheet with all the adjudicated endpoints. SCI will merge the data from the various files into one SAS dataset.

The analysis will proceed in the following steps:

8. SCI will prepare a spreadsheet summarizing each trial's method of collection of baseline variables.
9. For each trial, SCI will elicit information on how study drug was stopped and on follow-up of participants after they stopped study drug.
10. The Steering Committee will agree upon definitions for "time on study" for each of the trials.
11. SCI will create analysis datasets incorporating these definitions. It will send the analysis datasets to each individual trial's Steering Committee for review.
12. The Steering Committee will use uniform definitions of baseline variables (e.g., race/ethnicity, cardio- and cerebrovascular risk factors).
13. SCI will analyze each trial's data in accordance with the analytic plan. It will send the results of those analyses, along with any SAS code requested by the Steering Committees, to each trial's Steering Committee.
14. After each trial's CTSA Study Representative has reviewed the analysis from its own trial, SCI will proceed with a pooled analysis.

SCI has quality assurance mechanisms in place to ensure the scientific and statistical validity of all its programs and reports. Statistical analyses, analytic programs, and data sets are all audited in conformance with SCI's proprietary in-house *Data and Programming Guidelines*. SCI thoroughly reviews its reports for accuracy.

Janet Wittes, Ph.D. will assume statistical leadership for SCI. Robert Fowler, M.S., will serve as Project Manager and primary statistician. Gretchen Arndt will serve as Project Coordinator. She will be responsible for collecting and summarizing the baseline data. Dr. Wittes, Mr. Fowler, and Ms. Arndt will write the statistical report summarizing the results. Sara Jimenez, M.S., will write some of the SAS programs.

Please refer to the Statistical Analysis Plan, under separate cover, for further details.

III. Clinical Endpoint Center: Standard Operating Procedures

NOTE: Clinical Endpoint Center Policies and Procedures (P&P) are generally considered internal documents meant to document and describe the Center's Standard Operating Procedures for running a Clinical Endpoint Committee. A complete listing of all P&Ps are maintained on file in the Clinical Endpoint Center. Certain key polices pertaining to the operating principles of this project are described below.

A. Event Review Process and Committee Meetings

It is the policy of the CEC that for each meeting whereby the Physician Reviewer meets with the Chairman to discuss event criteria or the adjudication of a specific event(s), that minutes be recorded. Both Physician Reviewers (Drs. Solomon and Finn) need to be present in order to constitute a Committee Meeting. Meeting minutes will be transcribed in detail by the Project Coordinator and distributed to the CEC Project Manager for approval. The final minutes will be distributed to all CEC staff. Finally, a log will be kept of all such meetings; all meeting documentation will be kept on file in the project's Central Study Binder and individual Physician Reviewer Binders available to both Drs. Solomon and Finn.

Dr. Finn will provide primary review of the event and will ensure the proper source documentation has been received. Dr. Finn will then present his findings to Dr. Solomon who will also review the event. After the event has been discussed and reviewed by both Drs. Solomon and Finn, the adjudication form will be completed with the agreed-upon event classification.

B. Consistency Guidelines: Case Precedence Listing

It is the policy of the CEC that all events be reviewed and classified in a consistent manner throughout the project. Drs. Solomon and Finn have collaborated on numerous CECs over the past 7 years and have a cohesive working relationship that supports consistent event adjudication in this project. Another way consistency is achieved in this project is via a Case Precedent Listing. Clinical staff responsible for event review and adjudication must refer to this listing to be sure a precedent has not already been set for a similar event currently under review. During a Committee meeting, Dr. Solomon will dictate new case precedents, prn. This dictation is transcribed by the CEC Project Coordinator, approved by the Chairman, inserted into the appropriate section of Case Precedence Listing and distributed to CEC staff. The Case Precedence Listing is organized into various sections for easy reference and retrieval of previous Committee decisions. Finally, this list may also contain general notes on a certain topic and may not necessarily need to refer a particular event. The most recent version of the Case Precedent Listing is filed in the Central Study Binder and individual Physician Reviewer Binders.

C. Document Control: Central Study Binder & Physician Reviewer Binder

It is the policy of the CEC that all pertinent materials related to the review of events be filed in a project's Central Study Binder (CSB) as well as Physician Reviewer Binders. Such documentation will include but is not limited to: final CEC MOP, copies of all Event Screening Logs, Event Shipment Logs and Adjudication Shipment Logs, Case Precedent Listing, Meeting Minutes and Reviewer Memos, CTSA Teleconference Meeting Minutes, CEC Reports, final copies of the CEC adjudication form and internal administrative work instructions.

D. File Storage & Security

It is the policy of the CEC that all study-related administrative material (SOPs, other documentation) be maintained in the CEC and filed in areas under the direct supervision of project staff. Once event-specific data are distributed, Physician Reviewers have the responsibility for this material and for ensuring that all event-specific data are returned to the administrative project staff for proper filing and storage. All event-related study material is also kept on file in the CEC in a locked cabinet.

All study events will be stored by the CEC for at least 5 years after study close. At that point, events will either be stored at an off-site storage facility or returned to NCI.

All electronic data are stored on a CEC shared network accessible only by staff employed by the CEC. The Center is accessed only by key-pad and locked during non-business hours.

E. CEC Blinding: Patient Identifiers & Treatment

In compliance with the HIPAA, it is the policy of the CEC that all patient identifiers be thoroughly blinded prior to shipment to the CEC. Should the CEC become unblinded to a patient's identification, efforts will be made at the CEC to blind the information and notify the CCSA of the occurrence.

To ensure the unbiased review of events, it is the policy of the CEC that diligent efforts will be made by any group responsible for sending data directly to the CEC to thoroughly blind any data associated with treatment assigned, relatedness of event to study drug, study medication dosage and any other information that may potentially bias the event review process at the CEC. Should the CEC become unblinded to this information, efforts will be made to promptly black-out the data in question and these instances will be documented in a memo to the group sending the CEC the event in order that additional efforts are made to ensure proper blinding.

F. Event Adjudication Documentation

It is the policy of the CEC that Physician Reviewers be required to provide adequate and appropriate documentation of the details surrounding each event and the rationale and/or justification for the event's adjudication. This documentation is done primarily on each adjudication form, but additional documentation may also be provided on the Event Review Form (ERF). The ERF is an internal CEC worksheet used specifically for CEC use. Distinct from the ERF, the adjudication forms are considered official forms on which the CEC will document its final adjudication of each event. After completed adjudication forms are turned in, the CEC Project Manager reviews each event before it is filed to be sure adequate explanation and details are provided on the adjudication form and ERF. Documentation should also exist that reflects what was discussed during a Committee meeting and whether any Case Precedents were cited.

G. CEC Staff Training & Expertise

It is the policy of the CEC that all members be adequately trained on the objectives of each study. All CEC members will receive appropriate study/project training prior to the first submission of endpoints that will include the following:

- Overview presentation of the protocol (if applicable) and/or project's objectives
- Clarification of event classification/adjudication criteria
- Explication of the endpoint package contents and final adjudication form submission
- Overview of the project scope including event review process, key stakeholders, anticipated workload
- Familiarization with adjudication conventions (*e.g.*, completion of adjudication forms, requests for additional documentation)
- Hospital-mandated HIPAA training
- Hospital-mandated NIH Human Subject Research Certification

IV. CTSA: CEC Operations

NOTE: As mentioned previously in Section II.C., CCSA will be responsible for sending events to the CEC. The exception to this is the ADAPT trial. The ADAPT Data Coordinating Center at Johns Hopkins will work directly with the CEC for the sending and receiving of ADAPT events and queries. Adjudication forms for all studies will be sent to CCSA. For ease, this distinction was not carried out in the sections below. Rather, CCSA is referenced as the source for working with the CEC. When the specific convention below concerns the ADAPT trial, CCSA will not be directly involved but rather the interface will be between the ADAPT team and the CEC project management staff. The ADAPT team maintains the same responsibilities as the CCSA team in what is outlined below.

For the project files, CCSA appreciates receiving copies of the ADAPT data listing, case documentation, and any relevant correspondence in the course of data collection and analysis with the ADAPT team.

A. Identification of Events to Send to the CEC: Event Screening Logs

Objective: Taking into consideration the uniqueness of each trial, the purpose of the Event Screening Log is to provide the CEC with a large pool of events from each study in order for the CEC to screen and identify the appropriate events to receive for further review and adjudication.

Methods: Each study received the same instructions and overview of the project's objectives and an explanation of what events the CEC will receive for review and adjudication. Given the uniqueness of each trial, the methods and process used in each trial to collect the data requested in the Event Screening Logs varied. See Appendix G for the instructions that were distributed to each study.

NOTE: Given the size and additional complexity of the ADAPT study, additional instructions and guidelines were provided by the CEC to gather the pool of events for which to populate the ADAPT Event Screening Log. Additional documentation describing the approach that was used is also listed in Appendix F.

Description: CCSA is responsible for sending the CEC an electronic listing of all reported events to January 31, 2005 (the cut-off date planned for the CTSA analysis) for MA27, NEI, and SelCel studies. Care will be taken by CCSA and each respective study in generating this list to be sure that each Event Screening Log that is sent to the CEC:

- a) is complete and does not contain missing or ambiguous data; the data is also checked for any potential unblinding information.
- b) contains the most up to date information related to exactly what has been reported in the form of events (*i.e.*, if a site initially reported pneumonia for cause of hospitalization, but later revised it to lung cancer as the cause of admission, the CEC should be aware that lung cancer is listed as the cause of admission.)
- c) does not contain duplicate information already received. As new events are reported, the CEC should receive updated listings of ONLY the new events that have been added or previously reported events where there has been a change in reported term* (see example above).
- d) for any changes/updates that are made to any datum after it has been reviewed and returned by the CEC, such changes must be clearly indicated as to what field has been changed directly in the spreadsheet (*i.e.*, color coded for changed fields).
- e) contains ONLY data pertinent to the CEC. See Section VI.A. for the specific data that are required to be received in this Event Screening Log. To avoid potential bias no information related to treatment assigned, causality, action taken with study drug, etc. should be sent to the CEC.

It is critical that these listings are sent in an organized manner. Great attention to detail should be paid to ensure the CEC receives thorough, accurate information so that, for example, the same event is not reviewed twice.

Dr. Peter Finn will be responsible for providing this review of electronic listings. Using the Event Screening Logs, if Dr. Finn determines that a reported event has any potential to be cardiovascular in nature, the CEC will

flag the event and request information to be received for full review and adjudication. The Project Manager will be responsible for:

- receiving the event listings from CCSA and ensuring they are organized in a clear manner and formatted consistently
- distributing the list to Dr. Finn and ensuring that the events of interest are appropriately flagged
- ensuring the Event Screening Log is returned to CCSA in a reasonable timeframe.

*CCSA should develop a clear and consistent method for communicating any changes to a study's Event Screening Log after an event has already been screened by the CEC so it is clear a) what EVENT is being re-reviewed, b) what data have changed and why and finally, c) what our previous determination was.

With the understanding that not every study will collect the information below or if the information is collected it may not be databased; the following list is a **general description** outlining what should be included in each study's Event Screening Log:

1. Patient ID Number
2. StudyID Number
3. Unique Event ID Number
4. Date of Randomization
5. Site Reported Event Onset Date
6. Site Reported Event Resolution Date
7. Site-Reported Event/Event Description
8. Site-Reported Narrative (ie as completed on a study's reporting form)
9. Study Reported Investigator Term
10. Study Reported Event Outcome
11. Study Reported Event Severity
12. Study-Reported Event/Event Description
13. Study-Reported Narrative (ie as completed on a study's reporting form)
14. Comments

Per-Study Event Screening Logs are kept on file at the Clinical Endpoint Center.

B. Sending Events to the CEC: Event Shipment Logs

Objective: The purpose of the Event Shipment Log is to provide a clear tracking mechanism for the events sent by CCSA to the CEC.

Methods: Whenever a shipment of events is sent to the CEC, an Event Shipment Log will be sent to the CEC (electronically in advance of the shipment and a hard-copy in the actual shipment) in order to cross check the events actually received with what CCSA believes it has sent.

Description: CCSA is responsible for sending all events to the CEC in a clear, organized and consistent manner. The CEC Coordinator will merge data from the Event Shipment Log directly into the CEC's internal tracking database. Once all events are received, the Coordinator ensures that all events listed on the Event Shipment Log were in fact received and sends CCSA the Event Shipment Log back with a 'CEC Confirmed Receipt' column completed for all events received. Any discrepancies will therefore be immediately identified and resolved promptly. This process avoids manual data entry mistakes, keeps clear the data the CEC is receiving and maintains a smooth and efficient process for sending and receiving events.

Events will be sent to the CEC with the following principles in place:

- a) all events will be sent to the CEC in the form of a labeled manila folder* and sent via traceable courier.
NOTE: Email text messages regarding specific events should be avoided.

- b) all events that occur in one patient will be filed in one folder. If the CCSA has already sent the CEC an event on a particular patient, event documents should be carefully clipped together and sent to the CEC without a folder. The CEC will find the folder that has already been sent and file the new event documents in the established folder for review.
- c) all events that occur in one patient in the same setting should be sent together in the same shipment to the CEC. Although this will result in some delay, it will greatly reduce rework by the CEC; provide the CEC with a complete picture of all events during review, and reduce potential queries to the CCSA if other events were not sent
- d) ideally, all events that occur in one patient should be sent in chronological order. For example, if a patient's death event is ready to be sent but the stroke documentation from a month prior to the death is not ready, it is most practical and efficient if the CEC receives a patient's events in chronological order.
- e) events should not be sent to the CEC until ALL required documents (See Section IV) have been received for each event. CCSA should wait to send an event to the CEC until it has received all required documents and only when it is reasonable to assume that additional information/source documentation is not going to be forthcoming from the sites.
- f) if additional information/medical records are obtained (as a result of a CEC-generated query or not) or certain additional data become available after the initial chart/event has already been sent to the CEC, this information should be forwarded to the CEC via fax or traceable courier along with a written description of 1) what is being sent (unique event ID and what documents/data are included), 2) why it is being sent (*e.g.*, query response or the site suddenly found additional documentation that otherwise was not able to be obtained after exhaustive measures were taken or the site or safety personnel decided to change study data, such as event term).
- g) does not contain duplicate information already received. The CCSA needs to be careful not to send events twice. * Top tab manila folder, tab is labeled with the patient ID, all event documents are filed to the right of the folder, held in the folder by a top 2-hole punch/fastener. Event documents should be ordered, per event, with source documents on bottom followed by the study forms and any safety review documents.

Generally, Event Shipment Logs should contain the following;

1. Patient ID Number
2. StudyID Number
3. Unique Event ID Number
4. Date of Randomization
5. Site Reported Event Onset Date
6. Site Reported Event Resolution Date
7. Site-Reported Event/Event Description
8. Date Sent to CEC
9. Date Received by CEC
10. CEC Confirmed Receipt

C. Sending Queries to CCSA: CEC Query Spreadsheets

Objective: The purpose of the CEC-CCSA Query Spreadsheets is to provide a consistent and trackable manner in which to send, process, and receive requests for additional information.

Methods: Requests for additional information will be made by the Physician Reviewers on the Event Review Forms. Requests will be entered in the CEC Access tracking database by the Project Coordinator and merged into an Excel spreadsheet. Such requests for additional information will then be sent electronically to CCSA.

Description: It should be the intent of all parties in the CTSA project should aim to reduce the number of queries and re-queries to the sites for additional information. If the principles are followed in the above section and the events arrive with complete information, the number of queries to CCSA, and subsequently the sites, will

be greatly reduced. In the event the CEC does require additional information to adjudicate an event, the CEC reserves the right to issue a query for this information.

When, and only when, a particular event's query is resolved, CCSA will complete the appropriate column in the query spreadsheet for that particular event and send it electronically back to the CEC. The CEC Coordinator will send and receive these query spreadsheets. This affords a clear and efficient system for tracking and documenting when a query was sent, what was queried, what the query response was and when the query was resolved.

Note: If the query response consists of additional documents that need to be forwarded to the CEC (courier or fax is acceptable) the CCSA staff should note on the query spreadsheet that "additional documents are being couriered/faxed to the CEC on *date*" and that will suffice for a query response.) The CEC Coordinator will merge this query and response into a Word document and together with any additional documents, the chart will be redistributed to a Physician Reviewer.

Generally, Query Spreadsheets will contain the following information:

1. Patient ID Number
2. Study ID Number
3. Unique Event ID Number
4. Date Received by CEC
5. Date Query Sent to CCSA
6. Query Description
7. Date Query Response Sent to CEC
8. Query Resolution

D. Sending Final Adjudication Forms to the CCSA: Adjudication Shipment Logs

Objective: The purpose of the Adjudication Shipment Log is to provide a clear tracking mechanism for the adjudication forms sent by the CEC to CCSA.

Methods: Whenever a shipment of adjudication forms is sent to CCSA, an Adjudication Shipment Log will be sent (electronically in advance of the shipment and a hard-copy in the actual shipment) in order for CCSA to cross check the events actually received with what the CEC believes to have sent.

Description: The final adjudication forms will be completed by Dr. Finn and signed by both Dr. Finn and Dr. Solomon as well as the Project Coordinator. The complete and signed forms will undergo a general quality assurance review by the Project Manager to ensure the form is complete and data are unambiguous. After the relevant tracking data are entered into the CEC's database, the Project Coordinator will generate the Adjudication Shipment Log and send the completed forms to CCSA via traceable courier. Once the shipment of adjudication forms is received by CCSA, CCSA will in turn be responsible for sending the CEC an electronic 'confirmed receipt' in the appropriate column in the Adjudication Shipment Log to signify that all events sent were in fact received.

Generally, Adjudication Shipment Logs will contain the following information:

1. Patient ID Number
2. Study ID Number
3. Unique Event ID Number
4. Date Event Sent to CCSA
5. CCSA Confirmed Receipt
6. Date of CCSA Confirmed Receipt

VI. Required Data for Each Event

It is the policy of the CEC that adjudications be based on at least one supporting source document per event. This supporting source document is a medical record or note **provided by and/or from the enrolling or treating site that is independent of the study-produced event report or medical monitor report.** In these

trials, the source documentation collected for each event may vary widely. It is generally accepted that a discharge summary or physician narrative will be the most likely supporting source document. The CEC will make every effort to adjudicate events in a consistent manner using the data that are provided. In some instances, additional source documentation may be requested if data provided are misleading or not sufficient for consistent adjudication across all events.

Although variations will occur from study to study, the generally accepted required documentation to receive for each event is as follows:

A. **Site Event Case Report:** This should consist of all data provided by the site on a study's specific event reporting form(s). The CEC only needs to be provided with the most up to date and current copy of the event reporting form(s).

B. **Safety/Monitor Event Summary/Report:** This should consist of a study's Safety Group's review and report on what occurred in relation to the reported event. The CEC only needs to be provided with the most up to date and current copy of this report and related forms.

C. **Source Documentation/Medical Records :** The CEC should be provided with all medical records provided by a site when the event was initially reported. In addition to this and/or taking this into consideration, the CEC must also receive at least one source document, preferably and most frequently a Discharge Summary, **from the treating physician and/or admitting hospital**. If this is not available then a Physician Narrative from either the treating physician or enrolling site should be provided. NOTE: Source documentation originating from the enrolling site is acceptable when the enrolling site is the treating physician or facility where the event occurred or, when after determined effort, documentation originating from the enrolling site is the only information that is able to be obtained. The CEC would welcome additional source documents over and above a Discharge Summary/Physician Narrative, such as imaging reports for strokes, cardiac marker lab reports for ACS events, autopsy reports and any other source document that provided additional data to support the reported event.

VII. Unique Event Numbers

It is the policy of the CEC that each event reviewed be assigned a unique number in order to avoid any ambiguity or confusion when adjudicating events. For example, if the patient has two MIs during the same hospitalization, the identifier for the 1st MI must be clearly different from the identifier for the 2nd MI; all identifiers in a given trial should be unique. This unique number will either be provided by the trial, if the trial generally allows for unique event numbers, or, if not, CCSA will be responsible for generating these unique event identifiers.

VIII. Quality Assurance

It is the policy and primary objective of the CEC to provide a high-quality service and to remain consistent in event classification for all events received. The CEC will conduct all of its operations under the International Good Clinical Practices (GCP) and FDA guidelines. This MOP should be considered the Standard Operating Procedures for this particular study although more in-depth administrative work instructions may be produced for CEC's internal purposes.

Each member of the CEC will follow these SOPs. Any deviations will be documented by the Project Manager and if appropriate, communicated to NCI and/or CCSA. The CEC and its operations are subject to review by the FDA and other regulatory authorities, all records will be retained by the CEC for the length of time deemed necessary per the NCI.

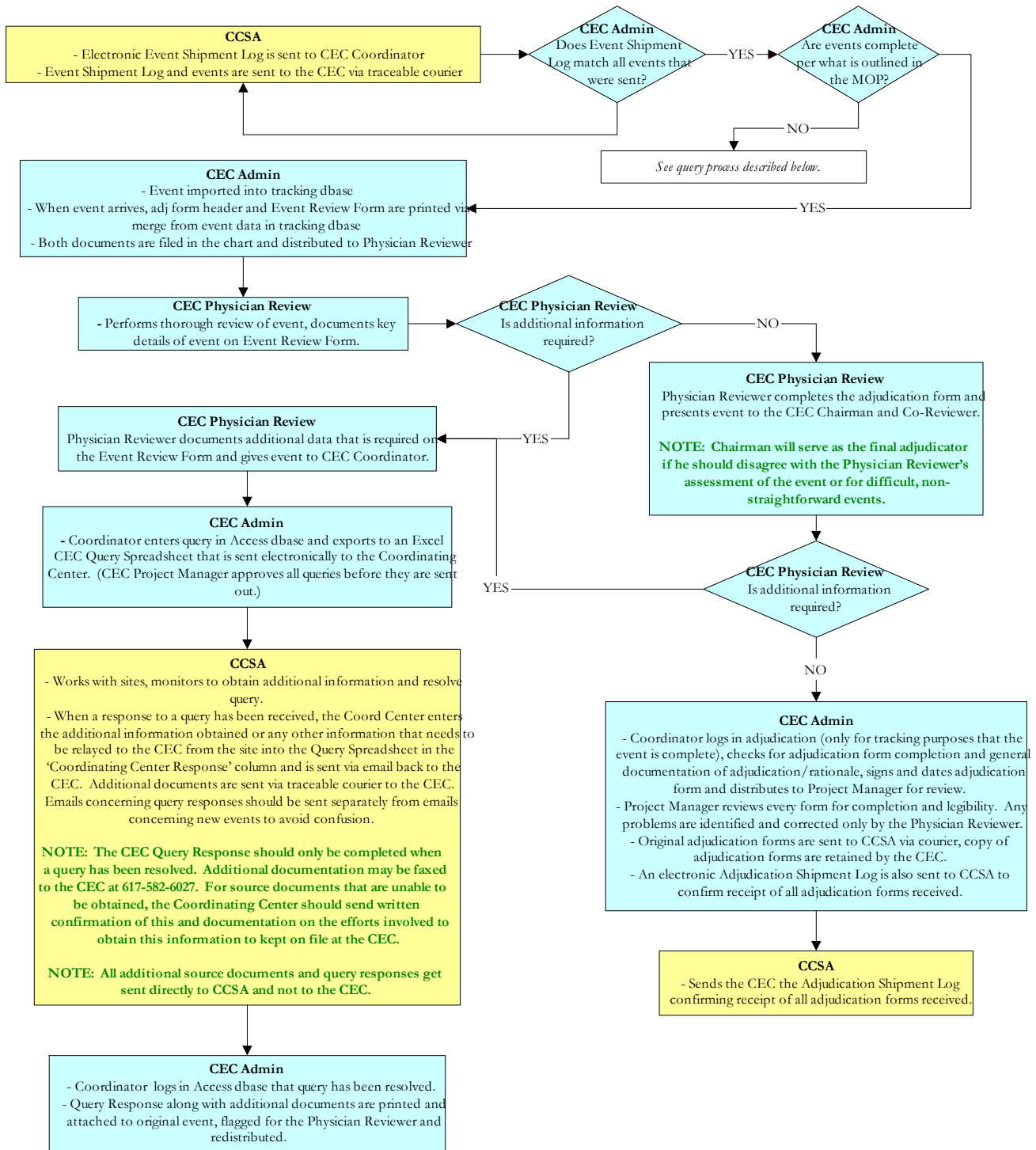
APPENDIX A: Adjudication Form Completion Instructions/SOPs

The final adjudication form for this trial is maintained under separate cover at the CEC. The following instructions and completion guidelines are in place with respect to the CTSA CEC adjudication forms:

- Each form is designed to record the adjudication of one event. The form's header is populated by the CEC Administrative Staff via a direct merge from the CEC database. Data from the CEC database are provided by CCSA in the Endpoint Shipment Logs. Each form consists of two pages. Each page of each form contains the patient's study identification to avoid any ambiguity regarding the identity of an event..
- Only Dr. Solomon and Dr. Finn are allowed to enter data on the forms; no administrative personnel or persons not associated with this project or the CEC will be providing any data on these forms.
- Each form contains the following five components:
 - I. Event Classification & Date of Event
 - Event Classification CV or Non-CV check box must be checked.
 - Clinical Documentation reviewed check boxes must be completed.
 - Question 3 in this section regarding whether the adjudicated date of event differs from the site-reported date of event must be checked and if the date does differ, the adjudicated date of event must be filled in.
 - II. Event Sub-classification & Specific Adjudication
 - One (and only one) check box from A-J must be checked to signify the event's sub-classification.
 - The questions must be thoroughly answered under the section that is checked.
 - 'Free-text' responses should be avoided.
 - III. Composite Events
 - Either Yes/No check box must be completed for each event. If a Composite Event did occur, the specific composite event and composite event date must be completed and clearly written.
 - IV. Additional Details & Justification
 - Drs. Solomon and Finn will provide a brief synopsis and general notes regarding the event's classification. Generally, some description of the event, event criteria and/or adjudication should be contained here for each event.
 - V. Comments/Signature
 - There is a line provided if any additional information or comments needs to be made regarding the event that is not otherwise captured elsewhere on the form.
 - There are signature lines for Drs. Solomon and Finn as well as a CEC Administrative Staff member to sign and date the forms. It is the policy of the CEC that by signing the forms, the person signing is attesting to the correctness and accuracy of the information on the form.
- These forms will be checked for completeness by the CEC Administrative Staff mentioned in Section II. Administrative Staff are responsible for signing each form once the appropriate quality check has been completed. Any omissions, general completion errors or ambiguities in how each form was completed will be brought to the attention of Dr. Finn in order that the appropriate correction may be made.
- As mentioned above, original forms will be sent via courier to CCSA. The CEC will retain copies of all forms sent. Should any changes need to be made to an event's form after the original has been sent to CCSA, Drs. Finn or Solomon will make an appropriate correction on the form, then initial and date the

change. The CEC Administrative Staff will copy the corrected form, send the 'wet ink' copy of the corrected form to CCSA and retain a new copy of the form.

CTSA CEC Event Review Process Diagram



APPENDIX C: Death Classification & Non-Fatal Event Criteria

The classifications made by the Endpoints Committee will be based on widely accepted criteria, utilizing supporting source documentation and the clinical judgment and expertise of the Endpoints Committee. The criteria for some of the events classified by the CEC are listed below as a general guide for classification and adjudication.

I. DEATH CLASSIFICATION

The CEC will determine the most likely cause of death. The cause of death will be the underlying cause, not the immediate mode of death. Death will be classified in three categories, Cardiovascular, Non-Cardiovascular or Unknown.

Death will be classified in the following categories:

A. Cardiovascular Death

Cardiovascular death is defined as follows:

Fatal Myocardial Infarction:

Fatal myocardial infarction may be adjudicated in any one of the following three scenarios:

- Death occurring within 14 days after a documented myocardial infarction in which there is no conclusive evidence to another cause of death. Subjects who are being treated for myocardial infarction and die as a result of complications of this myocardial infarction (*e.g.*, sudden death, pump failure or cardiogenic shock) will be classified as having a myocardial infarction related death.
- Autopsy evidence of a recent infarct with no other conclusive evidence of another cause of death.
- A Fatal Myocardial Infarction may be adjudicated for an abrupt death that has suggestive criteria for an infarct but does not meet the strict definition of a myocardial infarction. The suggestive criteria are as follows:
 - Presentation of chest pain
 - AND one of the following:
 - ECG changes indicative of an acute injury, or
 - Abnormal markers without evolutionary changes (*e.g.*, subject died before a subsequent lab draw),
 - or
 - Other evidence of wall motion abnormality

Pump Failure:

Death occurring within the context of clinically worsening symptoms and/or signs of heart failure without evidence of another cause of death.

If worsening heart failure is secondary to MI, then MI should be listed as the primary cause of death given that the subject suffered a MI within 14 days of death (as above).

Sudden Death:

Death that occurred suddenly and unexpectedly in an otherwise stable subject.

Presumed Sudden Death:

Death that occurred unexpectedly in an otherwise stable subject in which the subject was last seen ≥ 24 hours before death and circumstances are suggestive of sudden death.

Stroke:

Death occurring after a documented stroke.

Procedure-Related:

Death occurring during a cardiovascular procedure (CABG, PTCA, other) or as a result of later complications related to the procedure within 15 days. (Example: A subject who had a CABG up to fifteen days ago, who developed a subsequent myocardial infarction requiring inotropes, and who later died will still be classified as procedural related death.) The exact procedure will be recorded.

Other Cardiovascular:

Death must be due to a fully documented other cardiovascular cause not included above.

B. Non-Cardiovascular Death:

Deaths will be considered non-cardiovascular if there is no compelling cardiovascular cause of death. Examples of Non-CV sub classifications will include: Pulmonary, Malignancy, Infection, Hepatobiliary, GI, Renal, Procedural, Accidental, Suicide, and Other.

C. Unknown

All other cases of death, in the absence of a clearly defined non-cardiovascular cause, will be classified as Unknown if no other cause, as described above, can be found. These will be considered non-cardiovascular for the purposes of this analysis.

II. NON-FATAL EVENT CRITERIA

A. Myocardial Infarction and Hospitalization for Unstable Angina

Myocardial Infarction will be adjudicated when there is a clinical syndrome consistent with myocardial infarction (*i.e.*, chest pain, pulmonary edema) and/or ECG changes consistent with an acute coronary syndrome in association with elevation of cardiac markers above the local upper limit of normal, or compelling angiographic evidence of acute myocardial infarction/coronary occlusion.

Unstable angina will be adjudicated when there is a chest-pain syndrome consistent with coronary artery disease with ECG changes, cardiac marker elevation not sufficient for adjudication of myocardial infarction, or a clinical scenario that is consistent with cardiac chest pain in a patient with known coronary artery disease.

B. Stroke

Stroke is defined as a focal neurological deficit (resulting from a vascular cause involving the central nervous system) of sudden onset that is persistent (generally defined as not reversible within 24 hours) and which is not due to a readily identifiable cause (*i.e.*, brain tumor, trauma). When an imaging study is available (or other clearly documented supporting source documentation), we will further differentiate stroke as hemorrhagic, non-hemorrhagic, or unknown, and use this information for adjudication.

Hemorrhagic: when there is documentation of a hemorrhage.

Non-hemorrhagic: when there is documentation a stroke occurred but a hemorrhage was not documented or seen on exam.

Unknown: when there is no clinical, radiological, or other substantial evidence to document either a hemorrhagic or non-hemorrhagic stroke but a stroke is believed to have occurred.

Transient ischemic attack (TIA) is defined as a focal neurologic deficit lasting less than 24 hours and without imaging evidence of a hemorrhagic stroke or infarct. TIA will be categorized separately from stroke.

C. Revascularization

Documented occurrence of a coronary revascularization procedure, including coronary artery bypass graft (CABG) surgery, or percutaneous coronary intervention (PCI) or peripheral revascularization procedure (Carotid, Peripheral, Renal arteries, AAA) will meet the criteria for this event.

D. Resuscitated Sudden Death

Resuscitated sudden death will be defined as a sudden death or cardiac arrest, with or without premonitory heart failure or myocardial infarction, that is resuscitated by cardioversion, defibrillation or cardiopulmonary resuscitation, and after which the patient regains consciousness, even briefly. This definition excludes known transient losses of consciousness such as seizure or vasovagal episodes that do not reflect significant cardiac dysfunction.

E. Congestive Heart Failure

Admission to the hospital with clinical evidence of congestive heart failure, including signs or symptoms of heart failure in association with specific treatment for congestive heart failure (*i.e.*, diuretic, inotropic support or vasodilator), **or** congestive heart failure complicating a hospital admission for another cause where congestive heart failure is a *major component* of the hospital admission.

III. COMPOSITE EVENTS

To be consistent with what was done by the CEC in the APC and Pre-SAP trials, additional unreported non-fatal events identified during CEC review of event documents which are temporally related to the reported event (*e.g.*, occurred during same hospitalization) and /or occur as consequence of or treatment for the reported event (*e.g.*, pacemaker implanted during hospitalization for arrhythmia) will be reported as a Composite event on the adjudication form.

If additional unreported events are identified by the CEC and are thought *not* to be temporally related to the reported event, the CEC may opt to generate a new, distinct event.

APPENDIX D: CTSA Adjudication Form Example

CTSA Project: Cardiovascular Safety Review: Brigham and Women's Hospital SAE Review and Adjudication Form
Unique Event #: Patient #: Site Reported Onset Date:
Site Reported Event:

Section I. SAE Classification & Date of Event

1. SAE Classification: CV Non-CV

2. Clinical documentation reviewed:

- SAE report Discharge summary Autopsy report H+P ER/EMT notes
- Progress notes ECG traces Stress test report Imaging report Physician narrative/ letter
- Lab Reports Cardiac cath report Op Note Death Certificate Other _____

3. Does the adjudicated event date differ from the site-reported onset date? No Yes → Adjudicated Date of Event: _____

Section II. Event Adjudication

A. DEATH

CEC adjudicated cause of death:

- A. CV (check one of the following): Fatal MI Fatal Stroke Pump Failure
- Sudden Death Presumed Sudden Death
- CV procedure-related: Specify: _____
- Other CV: Specify: _____

B. Non-CV: Specify: _____ C. Unknown

B. NON CV EVENT

a. Specify: _____

C. CORONARY REVASCULARIZATION

a. Procedure performed: PCI CABG Unknown Other: Specify: _____

D. ARRHYTHMIA

a. Arrhythmia classification: Bradycardia Atrial premature contractions Atrial tachycardia Atrial fibrillation / flutter

Ventricular tachycardia Unknown Other: Specify: _____

E. STROKE

- a. If event met CEC criteria for CV event, classify: Non-hemorrhagic Hemorrhagic Unknown
- b. Neurological signs / symptoms: Yes No Unknown
- c. Abnormal brain imaging study: Yes No Unknown
- d. Neurology consultation: Yes No Unknown
- e. Other: Specify: _____

F. OTHER CV

- a. Non-coronary revascularization: Carotid Abdominal Aorta Renal Femoral Other: Specify: _____
- b. Other Cardiac surgery: AVR/ MVR Pacemaker / Defibrillator Implantation Other: Specify: _____
- c. Thromboembolic event: Pulmonary embolus Venous thrombophlebitis Other: Specify: _____
- d. Cardiac Arrest/Resuscitated Sudden Death
- e. Other: Specify: _____

G. CONGESTIVE HEART FAILURE

- a. Hospital admission for the management of heart failure.
- b. Hospital admission for another reason in which the management of heart failure becomes a major component of hospital stay.

H. RESUSCITATED SUDDEN DEATH

(Sudden Death or Cardiac Arrest successfully resuscitated [consciousness regained] by cardioversion/defibrillation or CPR)

I. MI a. Clinical presentation: _____

b. Cardiac Markers (peak values reported below):

CK value: _____ / ULN: _____ Unknown Not Done

CKMB value: _____ / ULN: _____ Unknown Not Done

Troponin value: _____ / ULN: _____ Unknown Not Done

c. ECG changes: Significant new Q waves (or R waves in V₁ or V₂) Evolving ST-T wave changes in two contiguous leads
 New LBBB ST elevation
 Other: Specify: _____ None
 Unknown

J. HOSPITALIZATION FOR UNSTABLE ANGINA

a. Ischemic chest pain/symptoms prompting hospital admission? Yes No

b. Cardiac Markers (peak values reported below):

CK value: _____ / ULN: _____ Unknown Not Done Other: _____

CKMB value: _____ / ULN: _____ Unknown Not Done Other: _____

Troponin value: _____ / ULN: _____ Unknown Not Done Other: _____

c. ECG changes: ≥ 0.5 mm ST depression in two contiguous leads ≥ 2 mm T wave change in at least two contiguous leads
 ≥ 1 mm S-T elevation in two contiguous leads ≥ 0.5 mm STchange compared to most recent or stable trace
 (or S-T depression in V₁ or V₂) Other: Specify: _____
 Unknown

Section III. Composite Events

a. Is there a composite event identified in conjunction with the above reported event ?

No Yes → Specify Event: _____ Composite Event Date: _____

Section IV. Additional Details/Justification:

Comments: _____

Physician Reviewer Signature: _____ Date: ____/____/____

Physician Reviewer Signature: _____ Date: ____/____/____

CEC Administration Signature: _____ Date: ____/____/____



CTSA: CEC Event Review Form

Study: _____

Date Received by BWH: _____

Date Distributed to PF: _____

Screening Log Event Summary:

Site #	«Merge Record #»«SITE»
Patient ID	«PATID»
SAE ID	«saeid»
Date of Randomization	«randomdt»
Site Reported Onset Date	«onsetdate»
Site Reported Offset Date	«offsetdate»
Severity	«sevrad»
Severity Code	«SEVERcode»
Site Reported Event Description	«EVENTDES»
“Verbatim”	«verbatim»
Outcome	«outcome»
Narrative	«narrative»
Comments	«comment»

CEC Comments:

CEC Query: Date of Query Request: _____

*NOTE: This is an internal worksheet for CEC staff; CEC reserves the right to modify this form once the trial begins in order to achieve maximum efficiency and/or tracking of data relevant to review process.

APPENDIX F: ADAPT Initial Review and Screening of Events

Given the uniqueness and complexities in identifying appropriate events for CEC review and in order to do this in a thorough and systematic manner, the CEC Project Manager, on behalf of Drs. Finn and Solomon, worked directly with the ADAPT Coordinating Center in order to gain an appreciation for the ADAPT data collection forms and to then develop a strategy for identifying such events in a mutually agreed upon manner that elicits the best chance of collecting all events that should be sent to the CEC for review and adjudication.

All key communications and documentation regarding these discussions and resultant decisions are kept on file in the CEC's shared network folder: \\Sfa19\cec\$\CELEBREX\CTSA Trials\CTSA External Correspondence\ADAPT Event Identification.

APPENDIX G: CTSA Trials: Collection and Screening Instructions Per Trial

The CTSA Working Group, consisting of representatives from NCI, Stats Collaborative, CCSA and the CEC determined that a consistent message should be distributed to all trials participating in the CTSA project describing the CEC's role and key objectives in the CTSA project and specifically what events the CEC was looking to review. Moreover, it provided each trial with instructions on how to proceed in generating the first step in the CEC process; an Event Screening Log.

After review and approval by key members of the CTSA Working Group, the following letter was distributed to each trial's representative on 8/1/05.



August 1, 2005

Dear CTSA Trial Representative,

Members from the Brigham and Women's Hospital Clinical Endpoint Center (CEC), leading the Cross Trials Safety Analysis (CTSA) focused on the cardiovascular safety of celecoxib in placebo-controlled trials, will be responsible for reviewing all reported events in your trial that have the potential to be cardiovascular in nature or resulted in death. In order to get started with this review process and move forward in the most efficient and productive manner possible, we need to learn more about how each trial processes and codes the events of interest. As you know, our common goal is to accomplish this review by November of 2005 – we have much work to do and your assistance and cooperation with this process is critical to the project's success.

During the meeting in Bethesda, MD on July 20, 2005 it became clear that there was some confusion concerning the proposed screening log, which was generated directly from our experience in the APC and PreSAP trials. Your study most likely coded and recorded event data differently than the APC and Pre-SAP trials – *i.e.* with CTC 2.0 or 3.0. These differences aside, it is critical that we ensure that all events of interest to the CEC are submitted for review. We need your help in looking at your study's process and coding system in order to make certain that we capture all events of interest.

The purpose of this letter is to:

- a) clarify the CEC's role;
- b) provide examples of what types of events the CEC will receive for review and adjudication;
- c) provide examples of the types of electronic data (events graded as 3–5 based on CTC criteria) from each event that we would like to receive – by way of an “Event Screening Log”, Data on this electronic log would be generated from your study's database, pulled from a Case Report Form, or another form used to report these events (*i.e.*, an SAE form);
- d) provide examples of what types of paper documents will be needed from each event;
- e) gather information regarding what reporting method (and/or event dictionary) was used in each trial; *e.g.*, MedDRA, CTC.

At your earliest convenience, we request that you submit a sample “Event Screening Log” of 2 events from your study along with each event's supporting Case Report Forms and all other study forms used to document this event. Please e-mail or mail these documents to:

Email: dbagheri@ccsainc.com

Mailing Address:
Donya Bagheri, MS, DABT
Senior Director, Research and Development
CCS Associates, Inc. (also known as CCSA)
2005 Landings Dr.
Mountain View, CA 94043

Once we receive these samples from each study, the CEC and CCSA will review them and determine where commonalities exist and if necessary, tailor instructions for each study on how to format official Event Screening Logs.

After you have received confirmation on how to format the official Event Screening Log, you will be asked to send your study's Event Screening Log to CCSA. CCSA will then forward this log to the CEC, which will select events for review and adjudication

For example – the Event Screening Log may contain 500 events, 50 of which the CEC might determine to be in no way cardiovascular in nature (and therefore, not require more thorough review and adjudication). Weeding out these 50 events will result in less work by each study, which can then proceed to gather copies of study forms and other source documentation for the remaining 450 events.

The Event Screening Log therefore is a catalyst for the CEC event review and adjudication process.

The following information is provided to each study for use as a reference when determining what to include on the sample Event Screening Log and sample study forms:

A. Role of the Cardiovascular Safety Subcommittee

This Committee is charged with classifying all events that are potentially related to cardiovascular risk into Cardiovascular or Non-Cardiovascular categories. This Committee is further charged with providing this classification in an unbiased manner. **This means, the Committee is not interested in and should therefore be blinded to:**

- **treatment assignment**
- **whether an event is considered to be related to study drug**
- **general causality of an event.**

Studies are asked to keep this in mind when they are reviewing which events would be appropriate for the CEC to review.

B. Examples of What Types of Events the CEC Should Review

In general, studies are encouraged to report conservatively; if there is any uncertainty as to whether an event should be included on the Event Screening Log, please include it. The following list of events is not meant to be inclusive of all events but rather to provide a reference list or examples of the types of events the CEC is looking to screen, and potentially receive for review and adjudication.

- **All Deaths**
- **Coronary Revascularizations**
 - For Example: PCI, angioplasty, stent implantation, rotablation, coronary artery bypass
- **Cardiac Arrhythmias**
 - For Example: atrial or ventricular tachycardia, bradycardia, fibrillation, heart block, sick sinus syndrome
- **Strokes**

- For Example: CVA, ischemic/ hemorrhagic stroke, cerebral embolism, intracranial bleeding or hematoma, hemiplegia, TIA, any acute neurological event resulting in loss of function
- **Other Cardiovascular Surgery**
 - For Example: any percutaneous cardiovascular angioplasty or surgical revascularization including abdominal aneurysm repair, renal angioplasty, carotid angioplasty or endarterectomy, peripheral vascular angioplasty or bypass grafting, pacemaker/defibrillator implantation, cardiac valve repair or replacement
- **Thromboembolism**
 - For Example: deep vein thrombosis, thrombophlebitis ,pulmonary embolism
- **Congestive Heart Failure**
 - For Example: hospitalization for treatment of heart failure, volume overload, or pulmonary congestion, treatment for heart failure during a hospitalization for any cause, new onset heart failure, cardiogenic shock
- **Resuscitated Sudden Death**
 - For Example: cardiovascular collapse, cardiac arrest, cardio-pulmonary arrest or any sudden loss of consciousness requiring active resuscitation, CPR, defibrillation for restoration of circulatory function
- **Myocardial Infarction (MI)**
 - For Example: severe acute myocardial ischemia, elevated cardiac markers or enzymes, ST- or Non-ST-elevation MI, Q wave MI, non Q MI, thrombolysis, enzyme leak, troponin leak
- **Hospital Presentation for Unstable Angina**
 - For Example: Acute Coronary Syndrome, acute myocardial ischemia, crescendo angina, acute stent occlusion, severe chest pain, presentation to rule-out myocardial ischemia
- **Other Cardiovascular**
 - For Example: aortic dissection, syncope, worsening hypertension, palpitations, mesenteric ischemia

C. Electronic Data to Include in the Event Screening Log

The following is an example of the general information the CEC is looking to receive electronically in the Event Screening Log. Please keep in mind that without knowing each trial in depth, we are counting on you to think of other data fields that are not listed below that would be of interest to the CEC – and excluding information the CEC is not interested in as mentioned above in Section A. Also, we would appreciate confirmation if a data point below is not collected in your particular study, or if it is collected but it is only captured on paper form. If possible, please submit this sample file in MS Excel format:

- Patient Identifier
- Unique Event Identifier
- Date of Randomization
- Date of Site-Reported Event
- Date of Site-Reported Event Resolution
- Site-Reported Event Term
- Site Reported Event Severity/Code of Severity
- Site-Reported Result of Event
- Site Reported Narrative*
- Date of Study-Reported Event
- Date of Study-Reported Event Resolution
- Study-Reported Event Term
- Study-Reported Event Severity/Code of Severity
- Study-Reported Result of Event

- Study-Reported Narrative
- Comments

*This might consist of a study's Monitor, Sponsor's Medical Monitor, Safety Group, Outcome's Committee – or perhaps even all of these entities. If more than one group's assessment exists, the CEC would appreciate receiving all the information it can.

D. Paper-Based Documents to Provide with Each Event

As mentioned previously, to first learn more about each trial, we are asking each study to provide 2 examples from two events of Case Report Forms – *or any other study forms* – used to document event-related data. If your study classifies events into “adverse events” (AEs) and “serious adverse events” (SAEs), please select one relevant event from each of these categories so we can get a sense of the collections methods you employ for each of these. This will help orient the CEC to which data are being collected by each study.

Once the system becomes operational, for all events that the CEC would like to review, the CEC will need copies of the data being collected on study forms *as well as supporting source documents on each event*. It is the policy of the CEC that adjudications are based on at least one supporting source document per event. This supporting source document is a medical record or note provided by and/or from the enrolling site's physician or medical center providing care of a particular patient. To be clear, this source documentation must be prepared by persons independent of study personnel. In these trials, the source documentation collected for each event may vary widely. It is generally accepted that a discharge summary or physician narrative should be provided for each event. Other examples of common supporting source documents would be lab reports of elevated cardiac markers (for Acute Coronary Syndrome events) and imaging reports (for Stroke events). The CEC will make every effort to adjudicate events in a consistent manner using the data that are provided for each event. In some instances, additional source documentation may be requested if data provided are misleading or insufficient for consistent adjudication across all events.

NOTE: All data that are sent to the CEC need to be thoroughly de-identified, every page that is sent needs to be labeled with the patient's study identification (the CEC does not want to assume anything about what is sent if pages are not appropriately labeled) and all source documents need to be translated into English.

You will be notified which events to collect documentation on once the CEC has reviewed each study's Event Screening Log.

E. Study Reporting Methods

Along with your two case examples, we would also appreciate written confirmation from each study of the specific coding system and process that occurs when an event of the type mentioned above occurs. For example, some studies use the CPT coding systems and others use MedDRA; in some studies, all events are reviewed by a Safety Group before being reported, others are not. Please refer to the attached CTSA Adverse Event Information Checklist in MS Word.

To review, what is requested from each study is the following:

1. Sample “Event Screening Log” of two events (electronic spreadsheet). If relevant to your trial, one AE and one SAE are preferred.
2. Clarification if any of the requested sample data in Section C are either not collected at all, or are collected on a paper-based format only.
3. Sample of all CRF/study forms that collect data on the two sample events provided on the Event Screening Log.
4. Written explanation of the process and coding system used to report the types of events of interest to the CEC in your trial.

The CEC – and this entire project – will only be as good as the information it receives. We rely heavily on your cooperation and teamwork to help gather these data. If you should have any questions, you are welcome to contact the CEC directly; Renée Mercier, CEC Project Manager at 617-732-6993 or rmercier@rics.bwh.harvard.edu.

Sincerely,

Scott D. Solomon, MD, Chairman
Peter V. Finn, MD, Physician Reviewer
Renée Y. Mercier, Project Manager

for the **CTSA Working Group & Steering Committee**



**Cross Trials Safety Analysis (CTSA)
Celecoxib Project**

**CCSA
Manual of Operations**

*2005 Landings Dr.
Mountain View, CA 94043*

Version: 5/21/2007

CONFIDENTIAL

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I. Introduction

CCS Associates, Inc. (CCSA) will provide administrative and coordination support to the NCI's sponsored Cross Trials Safety Analysis (CTSA) project under a contract through SAIC. The CTSA project is a continuation of effort to the Brigham and Women's Hospital (BWH's) Clinical Endpoint Committee's (CEC's) analysis of the safety data for the APC and Pre-SAP trials. The scope of the CTSA project will cover further analysis of cardiovascular risks associated with celecoxib treatment for the following studies:

1. Adenoma Prevention with Celecoxib (APC) Trial
2. Prevention of Spontaneous Adenomatous Polyps (PreSAP) Trial
3. Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT)
4. Celecoxib and/or Selenium in Treating Patients With Adenomatous Colorectal Polyps (SelCel) Trial
5. Exemestane Compared With Anastrozole, With or Without Celecoxib, in Treating Postmenopausal Women After Surgery for Primary Breast Cancer (MA27 Breast Adjuvant) Trial
6. Treatment of Diabetic Macular Edema Trial (03-EI-0065)

Please refer to the individual protocol of each of the above trials for more information related to each trial.

II. Roles and Responsibilities

A. CCS Associates, Inc. (CCSA)

As mentioned above, CCSA will be responsible for providing coordination and administrative support to the project. These tasks include collecting and distributing documents and data listings as well as organizing and filing of the project data. Relevant to this MOP, CCSA will provide the following:

18. Create and maintain project team contact information; maintain project timeline.
19. Coordinate and communicate with the project team under NCI's direction.
20. Create templates for collection of the required SAEs and study data for analysis.
21. Collect the SAEs based on the required CEC's selection.
22. Collect additional study data based on the required data points for analysis.
23. Collect and as necessary review the supporting SAE documents (*e.g.*, case data information such as hospital discharge records).
24. Organize and maintain project files and collected data from the studies.
25. Prepare and submit the SAE Screening Logs, SAE Shipment Logs, and Adjudication Shipment Logs to CEC.
26. Prepare the labeled-manilla case folders; organize the required documents and ship to CEC.
27. Communicate with the study sites; process CCSA and CEC queries, as necessary.
28. Maintain tracking log files for the SAE Screening Logs, SAE Shipment Logs, and Adjudication Shipment Logs as well as the manilla case folders.
29. Develop and maintain a shadow file of the labeled-manilla case folders at CCSA.
30. Receive and process the Final Adjudication Forms.
31. Enter the Adjudication Forms data into the CTSA MS Access Database.
32. QC the data entered in MS Access Database.
33. Prepare CTSA Database in MS Access and send to SCI for analysis.
34. Store project documents, files, and electronic data.

Dr. Caroline Sigman has the overall oversight for the project.

Ms. Donya Bagheri is the Project Manager for this project and will provide support for all the coordination and communication activities under the NCI's directions (Tasks 1–5, 8, 10 and 11). Specifically, she will:

1. Create team contact information; maintain current information for the team.
2. Distribute all communications to the team under NCI's directions.
3. Prepare teleconference and meeting agendas and minutes.
4. Prepare study protocol and safety data listing templates
5. Communicate with the sites in collecting the required data and coordinate query resolution process.
6. Serve as main CCSA contact between NCI, SAIC, CEC and SCI project team.
7. Maintain the tracking files.

Dr. Linda Doody will work with Ms. Bagheri in collecting the required SAE case data as well as assist in query resolution process, as necessary (Tasks 4–6, 10).

Ms. Susan Thompson and Leona Baldonade will contribute to tasks 7, 9, 12 and 17 in organizing and maintaining the project files including the manila case folders for CEC review.

Mr. Dan Milgram will be responsible for maintaining the CEC study database and the IT system required for maintaining project electronic files. He will also prepare the required data sets for CEC submission as required under Task 16.

Ms. Amy Kelley under supervision of Mr. Milgram will process and enter the adjudication forms data into the CEC study database as outlined under tasks 13–14.

Ms. Robin Bravo under supervision of Ms. Bagheri contributed to the QC activities outlined under Task 15.

B. Clinical Endpoint Committee

The CEC is based out of Brigham and Women's Hospital Clinical Endpoint Center and is comprised of the CEC Chairman, a Physician Reviewer and administrative project staff. All members of the CEC are centrally located at Brigham and Women's Hospital which allows for close, consistent collaboration on this project. The CEC was responsible for providing event review and adjudication services for the APC and Pre-SAP trials; therefore, it was logical for the same group to be responsible for providing the same services to other trials using Celebrex.

For a description of CEC staff and their responsibilities, please refer to CEC's Manual of Operations attached to this report.

C. Science Applications International (SAIC) & National Cancer Institute (NCI)

SAIC will work as a government agent directly for the NCI and it will be responsible for administering the subcontract between SAIC and CCSA.

D. Statistics Collaborative (SCI)

SCI, which will serve as the statistical center for the CTSA, will have primary responsibility for analysis of the data on the cardiovascular safety for each of the six clinical trials to be included in this analysis. To that end, it will draft a data analysis plan to describe the planned statistical analyses for each trial and for the pooled analysis of all six trials. The pooled analysis will be based on individual patient data. Only after the CTSA Steering Committee has agreed upon the plan will SCI receive data from the trials.

Each trial will send SCI baseline and follow-up data as agreed upon above as well as its randomization list. CCSA will send SCI the final CTSA database with all the required adjudicated endpoints. SCI will merge the data from the various files into one SAS dataset.

The analysis will proceed in the following steps:

15. SCI will prepare a spreadsheet summarizing each trial's method of collection of baseline variables.
16. For each trial, SCI will elicit information on how study drug was stopped and on follow-up of participants after they stopped study drug.
17. The Steering Committee will agree upon definitions for "time on study" for each of the trials.
18. SCI will create analysis datasets incorporating these definitions. It will send the analysis datasets to each individual trial's Steering Committee for review.
19. The Steering Committee will use uniform definitions of baseline variables (e.g., race/ethnicity, cardio- and cerebrovascular risk factors).
20. SCI will analyze each trial's data in accordance with the analytic plan. It will send the results of those analyses, along with any SAS code requested by the Steering Committees, to each trial's Steering Committee.
21. After each trial's CTSA Study Representative has reviewed the analysis from its own trial, SCI will proceed with a pooled analysis.

SCI has quality assurance mechanisms in place to ensure the scientific and statistical validity of all its programs and reports. Statistical analyses, analytic programs, and data sets are all audited in conformance with SCI's proprietary in-house *Data and Programming Guidelines*. SCI thoroughly reviews its reports for accuracy.

Janet Wittes, PhD will assume statistical leadership for SCI. Robert Fowler, MS, will serve as Project Manager and primary statistician. Gretchen Arndt will serve as Project Coordinator. She will be responsible for collecting and summarizing the baseline data. Dr. Wittes, Mr. Fowler, and Ms. Arndt will write the statistical report summarizing the results. Sara Jimenez, MS, will write some of the SAS programs.

Please refer to the Statistical Analysis Plan, attached to this report.

E. CTSA Expert Panel

The following is a list of the CTSA Expert Panel:

Robert Califf, MD - Duke Clin. Research Institute, Duke U. Medical Center
Joel Greenhouse, PhD - Department of Statistics, Carnegie Mellon University
Ingram Olkin, PhD - Department of Statistics, Stanford University (ret.)

During the CTSA project, this panel provided guidance to the Steering Committee by reviewing the project procedures particularly, the Statistical Plan in preparation of the data analysis. Additionally, they provided input in finalization of the final study report as well as the manuscript prior to publication.

III. CCSA's Standard Operating Procedures

CCSA will follow project specific and standard company SOPs and guidelines to fulfill the requirements under this project. A complete list of the relevant SOPs and guidelines is maintained at CCSA's central SOP file.

A. Team and Project Meetings

CCSA will hold internal project teleconferences or meetings, as needed. No formal agendas or minutes are maintained for these meetings, unless necessary. For the project team teleconferences and meetings, a format has been established and will be followed. Examples of these documents are presented in Appendix A.

B. Project Templates

A number of project templates will be used for this project; these include:

1. Project timeline (CCSA): This initial timeline developed in MS Project describes the tasks and the associated timeframe for completing each task as presented under Appendix B.
2. SAE Listing Template (CCSA): Based on recommendations from the project team, CEC, SCI and NCI, a SAE Listing Template has been created for collection of all SAEs reported under each protocol. This template has been developed in MS Excel and the file is named: 'SAE Sample site listing 06152005.xls'. All project required SAEs would be selected by CEC based on a set of criteria as described in CEC's MOP.
3. SAE/Event Screening Log (CEC): The initial SAE listings collected in an Excel spreadsheet by CCSA and forwarded to CEC.
4. SAE Shipment Log (CEC): A tracking log accompanying the SAEs when they are forwarded to CEC by CCSA. This log only shows the new SAEs since the last shipment.
5. Adjudication Shipment Log (CEC): A log of CEC adjudication forms prepared by CEC and forwarded to CCSA along with the forms.

C. Central Study File

All project files are maintained electronically on CCSA's servers. These include copies of project timelines, study protocols, informed consents, CRFs, SAE listings, teleconference and meeting agendas and minutes, SOPs, guidelines, and templates. As necessary hard copies of project files will be available to CCSA's project team. These files will be maintained in a secure filing cabinet and treated as confidential.

D. System Security, Electronic and Hard Copy File Storage

CCSA staff has extensive experience in maintenance and storage of computer files and in compliance with the requirements set forth under AISSP Handbook, Part 6 of the HHS IRM Manual, will maintain project files. All personnel contributing to this project have satisfactorily completed NIH required computer training requirements. They have also completed the OHRP and HIPAA required requirements for handling sensitive and confidential data including patients' records.

All hard copy project files including SAE case folders are maintained in a locked and secure storage area. A daily check-out system and log are used for accessing the confidential data; this log is maintained by CCSA's administrative project staff.

All project files will be maintained by CCSA until 5 years after project closure. At that point, project files will either be stored at a secure off-site storage facility or returned to the NCI.

IV. CCSA Staff Training & Expertise

All CCSA staff have the necessary training and expertise to carry out the tasks outlined under this project, including the following:

- NIH–required HIPAA training
- NIH–required OHRP Certification
- NIH–required computer system training including handling sensitive information
- Involvement in CEC review of SAEs for the APC study, which followed similar processes
- Receipt and processing of all SAEs in NCI, DCP-funded studies

All members of this project’s have at least 5 years experience in carrying out similar projects including review, processing and adjudication of study events, specifically, most of the project team were involved in the APC and Pre-SAP trials with celecoxib.

V. Operational Flow for Processing SAEs

Appendix C shows the overall CCSA’s operational flow for processing SAEs; the details of each task is presented below.

NOTE: As directed by NCI, CCSA will be responsible for processing SAE listings and case documentation to CEC. The exception to this is the ADAPT trial. The ADAPT Data Coordinating Center at Johns Hopkins will work directly with the CEC for the sending and receiving of ADAPT events and queries. Once the data listings are finalized and the case documentation collected, they are forwarded to CCSA for processing and filing.

The cut-off date for the CTSA analysis for the NEI, MA27, Selenium and ADAPT study was January 31, 2005. For APC and Pre-SAP studies, the data were used per the previously published adjudicated analysis by CEC and SCI.

Create templates for collection of the required SAEs and study data for analysis. Collect the SAEs based on the required data points. Prepare and submit the SAE Screening Logs, SAE Shipment Logs, and Adjudication Shipment Logs to CEC.

As mentioned above, project templates have been created for collecting, logging, screening and selecting SAE cases as well as shipment of the case data.

Once the data is collected based on the SAE Listing Template, the following standard reporting data points will be forwarded to CEC for review and analysis based on established guidelines outlined in the CEC MOP:

1. Patient ID Number (PATIENTID)
2. Study ID Number (STUDY)
3. Unique SAE ID Number (UNIQUE SAE ID)
4. Patient enrollment date (ENROLLMENT DATE)
5. Date of Randomization (RANDOMIZATION DATE)
6. Study Reported SAE Onset Date (SAE ONSET DATE)
7. Study Reported SAE Resolution Date (SAE OFFSET DATE)
8. SAE event (EVENT)
9. Study Reported Investigator Term (RERPORTED TERM)
10. Study Reported SAE Outcome (OUTCOME)
11. Study Reported SAE Severity (GRADESEVERITY)
12. Safety/Monitor/MedDRA Body System Term (SOC (MedDRA Coding Only - Body System Term))

13. Safety/Monitor/MedDRA Preferred Term (PT (MedDRA Coding Only - Preferred Term))
14. Reason was SAE categorized as SAE (WHYSERIOUS)
15. Summary or description of the event (NARRATIVE)
16. Comments provided for the case (COMMENTS)

In advance of the shipments from CCSA to CEC, the shipment logs are used for notification. The SAE/Event Shipment Log is an Excel spreadsheet listing of all new events sent to the CEC's Project Coordinator electronically in advance of the actual SAE case shipment. Once all events are received, the CEC Coordinator ensures that all case data listed on the SAE Shipment Log were received and sends CCSA the SAE Shipment Log back with a 'CEC Confirmed Receipt' column completed for all events received. Any discrepancies will therefore be immediately identified and resolved in a prompt manner. This process avoids manual data entry mistakes, keeps clear the data the CEC is receiving and maintains a smooth and efficient process for sending and receiving events.

Collect additional study data based on the required data points for analysis.

As required by the SCI, additional protocol and per patient data are also collected for analysis. The SCI's templates and SOPs were applied for collection and processing of these data.

Collect and as necessary review the supporting SAE documents (e.g., case data information such as hospital discharge records).

Based on the policy of the CEC, adjudications are conducted based on at least one supporting source document per event; this supporting source document (e.g., medical record or note provided by and/or from the enrolling site that is over and above the SAE report or medical monitor report), will be collected and forwarded to the CEC. In the trials covered under the CTSA project, the source documentation collected for each SAE may vary widely. It is generally accepted that a discharge summary or physician narrative will be the most likely supporting source document. As pointed out in the CEC MOP, it is the goal the of CEC to adjudicate events in a consistent manner using the data that is already provided. In some instances, additional source documentation may be requested if data provided is misleading or not sufficient for consistent adjudication across all events.

Additionally, as noted in the CEC MOP, all data that is sent to the CEC thoroughly de-identified, every page that is sent will be labeled with the patient's study identification.

Prepare the manilla-labeled case folders, organize the required documents and ship to CEC. Organize and maintain the project files and the collected data from the studies. Develop and maintain a shadow file of the manilla-labeled case folders at CCSA.

Per CEC MOP, top tab manilla folder will be prepared. The tab is labeled with the patient ID and all SAE documents are filed to the right of the folder, held in the folder by a top two-hole punch/fastener. SAE documents are ordered, per event, with source documents on bottom followed by the study forms and any safety review documents.

It should be noted that for the ADAPT study, the CEC collected all the case data directly from the ADAPT study coordinator. CCSA received copies of all case data and organized them as described for the project files.

Maintain tracking log files for the SAE Screening Logs, SAE Shipment Logs, and Adjudication Shipment Logs as well as the manilla case folders.

As mentioned above, the tracking logs are prepared in advance of any data transmission or case file shipments to and from CEC. Electronic copies of these files are maintained within the project folder on CCSA servers.

Generally, Event Shipment Logs contain the following:

11. Patient ID Number
12. StudyID Number

13. Unique Event ID Number
14. Date of Randomization
15. Site Reported Event Onset Date
16. Site Reported Event Resolution Date
17. Site-Reported Event/Event Description
18. Date Sent to CEC
19. Date Received by CEC
20. CEC Confirmed Receipt

Query Resolution.

As outlined under the CEC MOP, all queries that are generated by the CEC and/or CCSA will be entered into the CEC tracking database, exported to Excel in the form of a query spreadsheet and received electronically by CCSA. CCSA will process the query and complete the appropriate column in the query spreadsheet for that particular event and send it electronically back to the CEC. The CEC Coordinator will send and receive these query spreadsheets through the CCSA's Project Manager. This affords a clear and efficient system for tracking and documenting when a query was sent, what was queried, what the query response was and when the query was resolved.

As instructed under the CEC MOP, if the query response consists of additional documents that need to be forwarded to the CEC (as email or courier or fax) the CCSA staff will note on the query spreadsheet that "additional documents are being emailed/couriered/faxed to the CEC on *date*" and this addition will suffice for a query response.)

Generally, Query Spreadsheets contain the following information:

9. Patient ID Number
10. Study ID Number
11. Unique Event ID Number
12. Date Received by CEC
13. Date Query Sent to CCSA
14. Query Description
15. Date Query Response Sent to CEC
16. Query Resolution

Receive and process the Final Adjudication Forms.

As outlined in the CEC MOP, all final adjudication forms will be completed and signed by the appropriate CEC staff and will undergo a general quality assurance review by the CEC Project Manager to ensure the form is complete and clearly recorded on the form. The CEC Coordinator will then send an electronic spreadsheet (Adjudication Shipment Log) to CCSA alerting them of the events expected to undergo adjudication. This Adjudication Shipment Log along with a cover letter (*e.g.*, email notification) and the original adjudication forms will be sent via traceable courier to CCSA. CCSA is responsible for sending the CEC an electronic 'confirmed receipt' in the appropriate column in the Adjudication Shipment Log that all events sent were received.

Generally, Adjudication Shipment Logs will contain the following information:

7. Patient ID Number
8. Study ID Number
9. Unique Event ID Number
10. Date Event Sent to CCSA
11. CCSA Confirmed Receipt
12. Date of CCSA Confirmed Receipt

Enter the Adjudication Forms data into the CTSA MS Access Database. QC the entered data in MS Access Database. Prepare final CTSA MS Access Database and send to SCI for analysis.

All Final Adjudication Forms will be received by CCSA's Data Management, logged in and tracked. All the data will be entered into the CTSA Database in MS Access; the structure of the database including the appropriate queries, forms, and reports have been developed by the CEC. CCSA is only responsible for data entry and QC per established guidelines. Following each batch of forms entry, the database was quality controlled 100% against the received source data. Discrepancies were addressed by CCSA Data Management and resolutions verified by the CCSA QA personnel.

Per CEC MOP, each reviewed SAE is assigned a unique number in order to avoid any ambiguity or confusion when adjudicating events. For example, if the patient has two MIs during the same hospitalization, it needs to be made clear for all involved what is the identifier for the 1st MI and what is the identifier for the 2nd MI; all identifiers in a given trial should be unique. This unique number will either be provided by the trial, if the trial generally allows for unique SAE numbers, or, if not, CCSA will be responsible for generating these unique SAE identifiers.

Each 2-page Adjudication Form contains the following five components; a sample of the form is provided in Appendix D:

- VI. SAE Classification & Date of Event
 - SAE Classification CV or Non-CV check box must be checked
 - Clinical Documentation reviewed check boxes must be completed
 - Question 3 in this section regarding whether the adjudicated date of event differs from the site-reported date of event must be checked and if the date does differ, the adjudicated date of event must be filled in.

- VII. SAE Sub-classification & Specific Adjudication
 - One (and only one) check box from A-J must be checked to signify the event's sub-classification.
 - The questions must be thoroughly answered under the section that is checked.
 - 'Free-text' responses should be avoided.

- VIII. Composite Events
 - Either Yes/No check box must be completed for each event. If Composite Event did occur, specific composite event and composite event date must be completed and clearly written.

- IX. Additional Details & Justification
 - Drs. Solomon and Finn will provide a brief synopsis and general notes regarding the SAE's classification. Generally, some description of the event, event criteria and/or adjudication should be contained here for each event.

- X. Comments/Signature
 - There is a line provided if any additional information or comments needs to be made regarding the event that is not otherwise captured elsewhere on the form.
 - There are signature lines for Drs. Solomon and Finn as well as a CEC Administrative Staff member to sign and date the forms. It is the policy of the CEC that by signing the forms, the person signing is attesting to the correctness and accuracy of the information on the form.

Following QC of the Final Adjudication Form by CEC's Administrative Staff, original forms are sent via courier to CCSA's Data Management. The CEC will retain copies of all forms sent. Should any changes need to be made to an event's form after the original has been sent to CCSA, Drs. Finn or Solomon will make an appropriate correction on the form, initial and date the change, CEC Administrative Staff will copy the corrected form, send the 'wet ink' copy of the corrected form to CCSA and retain a new copy of the form.

Store project documents, files, and electronic data.

CCSA will maintain all electronic and hard copy files for the project until 5 years after completion of the project. At that time, they may be stored off-site or returned to NCI or SAIC, as directed.

VI. Quality Assurance

It is the policy and primary objective of the CCSA to provide a high-quality service and to remain consistent with project MOP as well as applicable company SOPs and guidelines. Each member of CCSA's Project Team is trained to follow the project SOPs.

APPENDIX A: Sample Project Team Teleconference Agenda and Minutes

Cross-Trial Safety Analysis (CTSA) Teleconference Meeting Agenda
 Wednesday, June 29, 2005
 12:00 Noon–1:00 PM EDT

Dial in number is 866-680-0168
 Participant code is 488498
 Host: 173723 (For Drs. Viner and Hawk ONLY)

1. Discussion Points:

- Roll Call (E. Hawk, J. Viner)
- Status of study document collection (protocols, ICs, CRFs, Annotated CRFs, DSMB Plans/charters) (D. Bagheri, All)
- SAEs: Required data & listing – Data Cut-off date; Timeline for collection June 29, 2005- July 15, 2005 (D. Bagheri, All)
- Manual of Operations (CCSA, BWH, Stat Coll.)
- Statistical Plan (Stat. Coll.)
- Scheduling for face-to-face meeting at NCI (J. Viner, E. Hawk); July 20th and July 19th Dinner, Travel and meeting arrangements
- Backups to D. Bagheri July 5-July 18, 2005 – Kate Guyton and Caroline Sigman
- Next teleconference (instead would be the face-to-face meeting on July 20, 2005, 9-3 pm at NCI)

2. Action Items from previous teleconference:

				STATUS
6/15/2005	Bagheri	6/16/2005	Prepare and distribute teleconference minutes	Completed 6/16/2005
6/15/2005	Bagheri	6/15/2005	Provide copies of the protocols to Drs. Wittes' and Solomon's groups	Completed 6/15/2005
6/15/2005	Wittes/Bagheri	TBA	Contact each site to obtain more specific protocol information, as necessary	Will be initiated after review of the protocols
6/15/2005	Bagheri	TBA	Provide a format for collecting demographics and per patient data as required for analysis by Dr. Wittes/Solomon	Will be initiated after review of the protocols
6/15/2005	Viner	6/29/2005	Provide a data cut-off date for the SAE data analysis	In Progress
6/15/2005	Viner/Bagheri	6/30/2005	Provide additional information for the face-to-face meeting planned for July 20 th	In Progress
6/15/2005	Bagheri	7/20/2005	Provide a draft of the MOP	In Progress
6/1/2005	Wittes	7/20/2005	Provide a draft of the statistical plan for NCI's review	In Progress

				STATUS
5/4/2005	Solomon/ Wittes (Mercier)	7/20/2005	Provide requirements document and checklist for document collection and analysis similar to those for the APC and Pre-SAP analyses	Provided Draft Clinical Endpoint Committee (CEC) MOP for NCI and CCSA review 6/10/2005; being finalized
5/4/2005	Whitney	6/15/2005	Provide (1) data sharing agreements & (2) agreements to publish joint analysis	In Progress; drafts provided to Drs. Viner and Hawk for review; to be distributed for the July 20 th meeting
5/18/2005	Hawk, Viner	TBA	Selection of external review panel	In Progress

Cross-Trial Safety Analysis (CTSA) Teleconference Meeting Minutes
Wednesday, June 29, 2005
12:00 Noon–1:00 PM EDT

1. **Discussion Points:**

- Roll Call: The following participants were present for this call:
NCI: E. Hawk, J. Viner
BWH/CEC: S. Solomon, R. Mercier, P. Finn
ADAPT: B. Martin,
MA27/NCI Canada: J. Pater
SelCel: S. Obara
SAIC: J. Derge
CCSA: D. Bagheri, C. Sigman, L. Doody

- Status of study document collection (protocols, ICs, CRFs, Annotated CRFs, DSMB Plans/charters) (D. Bagheri, All)
Ms. Bagheri thanked everyone for providing the required study documents to her; all protocols, ICs, and CRFs (post telecom note: the CRFs for the NEI study were also received today). These documents have been forwarded to the BWH and Stat. Collaborative groups for review. The DSM plans and the DSMB charters are also being collected.

- Review of the SAE Required Data and Listings (D. Bagheri, All)
The SAE Required Data and Listing template has been finalized and was shared with the group. It was noted that all the data elements (*e.g.*, MedDRA coded data) might not be available for all studies, since there would be differences as to how the safety data were coded. For example, for the MA27 study, CTC version 3.0 is used for collection of the terms, and they are not coded any further. Dr. Doody mentioned that CCSA has a copy of the coding conversion (CTC version 3.0 to MedDRA version 6.0) file, if it would be useful. At this time, no further coding of the SAE data is planned.

The group also discussed the cut-off date for collection of the SAE data. This point is still under consideration, and a decision will be made in approximately one week. It was noted that the cut-off date for the APC and Pre-SAP analysis was 1/6/2005; approximately 2 business weeks after the last treatment dose on December 17, 2004. This date was also chosen due to the time frame for generating the NEJM publication for the February 2005 FDA meeting. Once a data cut-off date is identified, Ms. Bagheri will send an email requesting the SAE data in the template format. A tentative deadline for receipt of this data set was set for July 29, 2005. A smaller group *ad hoc* teleconference will be held amongst the NCI, BWH and Stat. Collaborative groups in the next week to discuss the SAE cut-off date and the additional per patient data elements required for analysis. The results of this call will be communicated to the team.

- Manual of Operations (CCSA, BWH, Stat Coll.)
The MOP will be developed primarily to document project procedures (BWH, Stat. Coll., and CCSA) and to specifically describe the adjudication and analysis processes applied by BWH. It is expected that drafts of the MOPs for each of these groups will be available by July 20th for the face-to-face meeting. The CEC MOP is under review and finalization; once the MOPs are available, they will be shared with each study investigator for review and ultimately to the External Review Committee for approval.

- Statistical Plan (Stat. Coll.)
As discussed in the June 15, 2005 teleconference, the MOP will represent the statistical plan and will be developed after review of the protocols; a draft is expected by July 20th.

Dr. Wittes and her colleagues will also contact each study site to further obtain study information following review of the collected documents.

- Status of Data Sharing Agreements
Dr. Hawk stated that a revised draft has been prepared and is currently under review. It will be circulated to the team for prior to the July 20 meeting.
- **The CTSA meeting in Bethesda has been scheduled for Wednesday July 20th, 2005 (9:00 am – 3:00 pm) and dinner on July 19th, 2005.** Travel and meeting details will be provided to the team shortly. The main purpose of this meeting is to coordinate activities in order to ensure timely execution of the cross-trials safety meta-analysis. Among other activities, the meeting will permit review and approval of the data sharing document, the MOP, and the statistical plan.
- **There will be no call on July 13th**; the July 20th face-to-face meeting replaces it. For those who cannot attend the Bethesda meeting in person, our usual teleconference number can be used to call into the meeting as listed below:

Dial in number is 866-680-0168
Participant code is 488498
Host: 173723 (For Drs. Viner and Hawk ONLY)

- Backups to Ms. Bagheri July 5-July 18, 2005 – Kate Guyton and Caroline Sigman. Please contact them for any CTSA related matters during this period. Their contact information is listed below:

Caroline C. Sigman, PhD President CCS Associates 2005 Landings Drive Mountain View, CA 94043 Phone: 650-691-4400ext 110 Cell: 650-906-4429 FAX: 650-691-4410/240-4013 email: csigman@ccsainc.com	Kate Z. Guyton, PhD DABT Director, Scientific Affairs CCS Associates 1741 Church St NW Washington, DC 20036 Tel 202-986-6244 Fax 202-986-6246 Mobile 202-365-8435 email: kguyton@ccsainc.com
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2. Action Items:

				STATUS
6/29/2005	Bagheri	6/30/2005	Prepare and distribute teleconference minutes	Completed 6/30/2005
6/15/2005	Bagheri	6/29/2005	Provide copies of all CRFs to Drs. Wittes' and Solomon's groups	Completed 6/29/2005
6/15/2005	Wittes/Bagheri	TBA	Contact each site to obtain more specific study information, as necessary	Will be initiated after review of the protocols and CRFs
6/15/2005	Bagheri	TBA	Provide a format for collecting demographics and per patient data as required for analysis by Dr. Wittes/ Solomon	Will be initiated after review of the protocols and CRFs
6/15/2005	Viner/Solomon	7/8/2005	Provide a data cut-off date for the SAE data analysis	In Progress

				STATUS
6/15/2005	Viner/Bagheri	6/30/2005	Provide additional information for the face-to-face meeting planned for July 20 th	In Progress
6/15/2005	Bagheri	7/20/2005	Provide a draft of the MOP	In Progress
6/1/2005	Wittes	7/20/2005	Provide a draft of the statistical plan for NCI's review	In Progress
5/4/2005	Solomon/ Wittes (Mercier)	7/20/2005	Provide requirements document and checklist for document collection and analysis similar to those for the APC and Pre-SAP analyses	Provided Draft Clinical Endpoint Committee (CEC) MOP for NCI and CCSA review 6/10/2005; being finalized
5/4/2005	Whitney	6/15/2005	Provide (1) data sharing agreements & (2) agreements to publish joint analysis	In Progress; drafts provided to Drs. Viner and Hawk for review; to be distributed for the July 20 th meeting
5/18/2005	Hawk, Viner	TBA	Selection of External Review Committee	In Progress

- Next teleconference (July 27th 2005; 12:00 NOON EDT)

Appendix B: Initial CTSA Project Timeline

ID	Task Name	Duration	Start	0	2001		2002		2003		2004		2005		2006		2007		2008		2009		2010	
				Qtr 3	Qtr 2	Qtr 1	Qtr 4	Qtr 3	Qtr 2	Qtr 1	Qtr 4	Qtr 3	Qtr 2	Qtr 1	Qtr 4	Qtr 3	Qtr 2	Qtr 1	Qtr 4	Qtr 3	Qtr 2			
1	Task 1 Project Initiation and Management	360 days	Mon 5/2/05																					
2	Draft and Finalize Project Timeline	7 days	Mon 5/9/05																					
3	Define project parameters, resources, work plan (includes timeline)	25 days	Mon 5/2/05																					
4	Set up SAIC contracts with CCSA, BWH, and Stat. Coll.	130 days	Mon 5/2/05																					
5	Establish project team and collect contact information	16 days	Mon 5/2/05																					
6	Establish data sharing agreements	73 days	Wed 7/20/05																					
7	Establish and finalize CCSA procedures and MOP	108 days	Wed 7/20/05																					
8	Establish and finalize statistical plan	60 days	Tue 9/20/05																					
9	Establish and finalize BWH-CEC MOP	103 days	Wed 7/20/05																					
10	Develop draft study matrix for data collection and analysis	6 days	Tue 5/10/05																					
11	Finalize study matrix for data collection and analysis	6 days	Wed 5/18/05																					
12	Conduct bi-weekly teleconferences	358 days	Wed 5/4/05																					
13	Prepare agenda and minutes for each teleconference	358 days	Wed 5/4/05																					
14																								
15	Task 2 Project Database Support	236 days	Fri 10/21/05																					
16	Define adjudication MS Access database standards	6 days	Fri 10/21/05																					
17	Design and test the database	7 days	Tue 11/22/05																					
18	Design and test the database entry screens	7 days	Tue 11/22/05																					

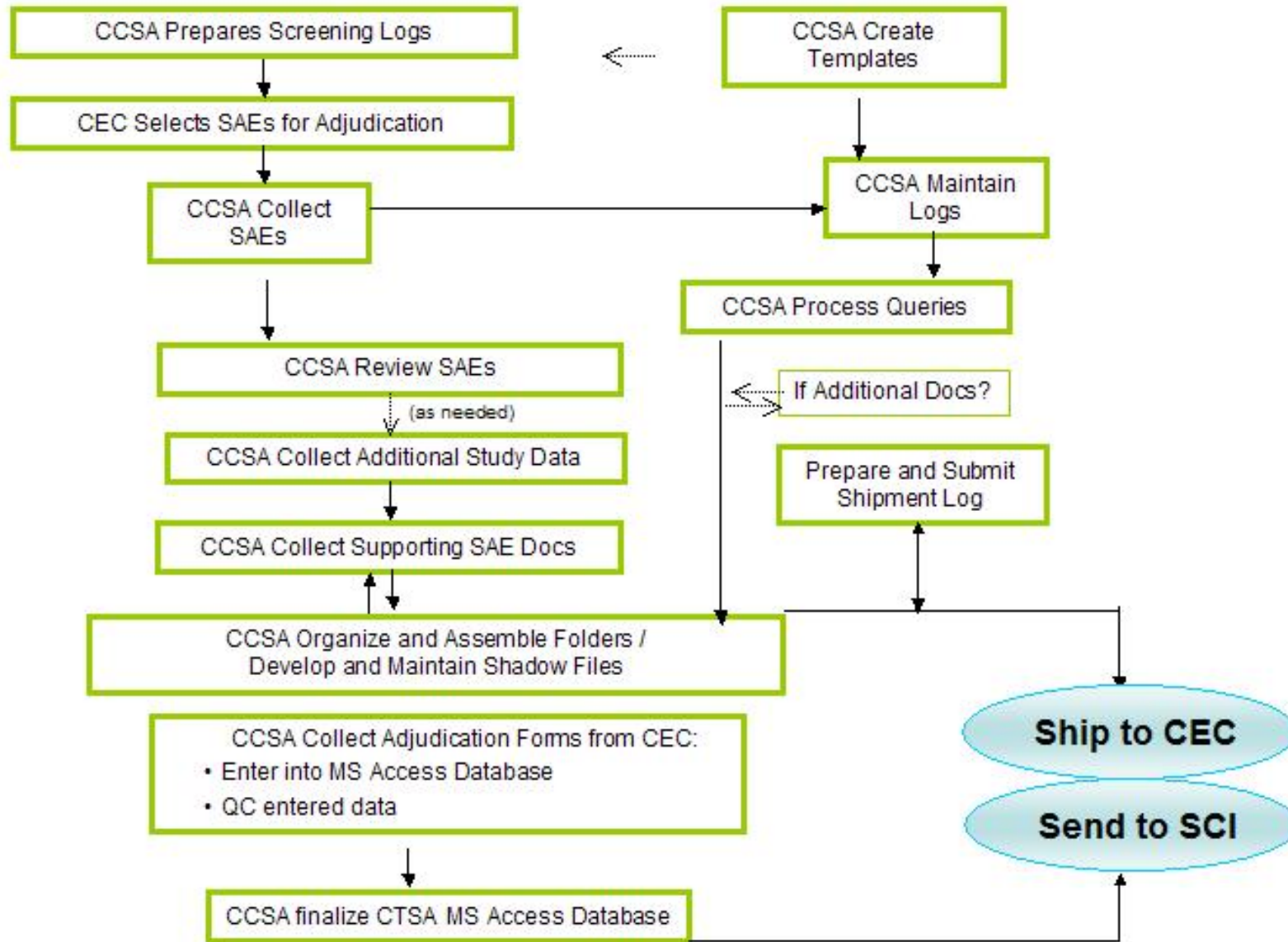
ID	Task Name	Duration	Start	0	2001		2002	2003		2004		2005		2006		2007		2008		2009		2010	
				Qtr 3	Qtr 2	Qtr 1	Qtr 4	Qtr 3	Qtr 2	Qtr 1	Qtr 4	Qtr 3	Qtr 2	Qtr 1	Qtr 4	Qtr 3	Qtr 2	Qtr 1	Qtr 4	Qtr 3	Qtr 2		
19	Design forms and reports	9 days	Wed 11/30/05																				
20	Train project team on data entry	2 days	Mon 12/5/05																				
21	Maintain system	214 days	Tue 11/22/05																				
22																							
23	Task 3 Data Collection, Entry, QC and	215 days	Mon																				
24	Data Collection	149 days	Mon 5/23/05																				
25	Communicate with main study sites; share study matrix requirements	1 day	Mon 5/23/05																				
26	Collect Study protocols, ICs, CRFs and DSMB documentation (charter)	11 days	Tue 5/24/05																				
27	Extract Protocol, ICs, and relevant CRF and DSMB charter data into study matrix Excel	15 days	Thu 7/21/05																				
28	Collect SAE Listings in MS Excel Format (Excludes ADAPT Listings)	28 days	Wed 8/24/05																				
29	Review SAE Listings (Excludes ADAPT Listings)	17 days	Mon 10/3/05																				
30	Organize SAE Listings (create case file folders per CEC MOP, Excludes ADAPT)	22 days	Wed 10/5/05																				
31	Query missing SAE information (Excludes ADAPT Listing)	21 days	Fri 10/7/05																				
32	Complete SAE case files (including review, QC and organization)	48 days	Wed 9/28/05																				
33	Prepare case files for shipment to BWH	45.2 days	Wed 10/5/05																				
34	Data Shipment to BWH/Review of Cases	118 days	Wed 10/5/05																				
35	Prepare shipment logs and ship the cases for CEC review	62 days	Wed 10/5/05																				
36	Receipt of cases and CEC Review	60 days	Fri 10/7/05																				

ID	Task Name	Duration	Start	0	2001		2002		2003		2004		2005		2006		2007		2008		2009		2010	
				Qtr 3	Qtr 2	Qtr 1	Qtr 4	Qtr 3	Qtr 2	Qtr 1	Qtr 4	Qtr 3	Qtr 2	Qtr 1	Qtr 4	Qtr 3	Qtr 2	Qtr 1	Qtr 4	Qtr 3	Qtr 2			
37	Address queries from CEC review	42 days	Thu 12/1/05																					
38	Re-review the cases and provide resolutions, as necessary	64 days	Tue 11/1/05																					
39	Complete Physician Review Forms	86 days	Mon 10/17/05																					
40	Submit Physician Review Forms to CCSA for data entry	53 days	Thu 12/1/05																					
41	Enter Physician Review Forms into MS Access Database	51 days	Mon 12/5/05																					
42	QC entered physician review data (10% of entered data)	12 days	Tue 2/14/06																					
43	Provide preliminary database transfer to CEC for review	1 day	Mon 3/6/06																					
44	Review database and request any other changes; freeze database for analysis	4 days	Tue 3/7/06																					
45	Prepare data listings from the freedzed database for statistical analysis; CEC to	5 days	Mon 3/13/06																					
46	Task 4 Data Analysis by CEC	207 days	Thu 12/1/05																					
47	Review SAE listings and reports for analysis	7 days	Mon 3/20/06																					
48	Request additional SAE information or listings, if necessary	5 days	Wed 3/29/06																					
49	Obtain additional requested SAE information or listings	6 days	Wed 4/5/06																					
50	Obtain baseline and randomization data by Statistical Collaborative for analysis	72 days	Thu 12/1/05																					
51	Finalize data listings for analysis	5 days	Mon 4/17/06																					
52	Perform statistical analysis of the data (version 0), distribute for review	46 days	Fri 4/21/06																					
53	Revise statistical analysis of the data (version 1) after review and receipt of comments from	11 days	Fri 6/23/06																					
54	Revise statistical analysis of the data (version 2) after review and receipt of comments from	11 days	Fri 7/7/06																					

ID	Task Name	Duration	Start	0	2001		2002	2003		2004		2005		2006		2007		2008		2009		2010	
				Qtr 3	Qtr 2	Qtr 1	Qtr 4	Qtr 3	Qtr 2	Qtr 1	Qtr 4	Qtr 3	Qtr 2	Qtr 1	Qtr 4	Qtr 3	Qtr 2	Qtr 1	Qtr 4	Qtr 3	Qtr 2		
55	Revise statistical analysis of the data (version 3) after review and receipt of comments from	11 days	Fri 7/21/06																				
56	Prepare draft of the manuscript	75 days	Mon 4/24/06																				
57	Review draft manuscript	13 days	Mon 8/7/06																				
58	Finalize manuscript	18 days	Wed 8/23/06																				
59	Task 5 Project Report	205 days	Mon 12/5/05																				
60	Draft format for report; include format for DSMB charter/DSMB plan data presentation	7 days	Mon 12/5/05																				
61	Distribute the report format for review; receive comments and implement for	18 days	Wed 12/14/05																				
62	Prepare preliminary report based on available data (background, rationale, study	15 days	Mon 1/9/06																				
63	Prepare a draft after results of the Statistical analysis and manuscript are	72 days	Mon 4/24/06																				
64	Review draft of the report	15 days	Wed 8/2/06																				
65	Revise the report, as necessary	7 days	Tue 8/22/06																				
66	Finalize report	11 days	Fri 9/1/06																				

Appendix C:

CCSA Operational Flow for Processing CTSA SAEs



Appendix D: Sample Final Adjudication Form

Section I. SAE Classification & Date of Event

1. SAE Classification: CV Non-CV

2. Clinical documentation reviewed:

- | | | | | |
|---|--|---|--|--|
| <input type="checkbox"/> SAE report | <input type="checkbox"/> Discharge summary | <input type="checkbox"/> Autopsy report | <input type="checkbox"/> H+P | <input type="checkbox"/> ER/EMT notes |
| <input type="checkbox"/> Progress notes | <input type="checkbox"/> ECG traces | <input type="checkbox"/> Stress test report | <input type="checkbox"/> Imaging report | <input type="checkbox"/> Physician narrative/ letter |
| <input type="checkbox"/> Lab Reports | <input type="checkbox"/> Cardiac cath report | <input type="checkbox"/> Op Note | <input type="checkbox"/> Death Certificate | <input type="checkbox"/> Other |

3. Does the adjudicated event date differ from the site-reported onset date? No Yes → Adjudicated Date of Event: _____

Section II. Event Adjudication

A. DEATH CEC adjudicated cause of death:

A. CV (check one of the following): Fatal MI Fatal Stroke
 Pump Failure

Sudden Death Presumed Sudden Death

CV procedure-related: Specify: _____

Other CV: Specify: _____

B. Non-CV: Specify: _____ C. Unknown

B. NON CV EVENT a. Specify: _____

C. CORONARY REVASCULARIZATION

a. Procedure performed: PCI CABG Unknown Other: Specify: _____

D. ARRHYTHMIA

a. Arrhythmia classification: Bradycardia Atrial premature contractions Atrial tachycardia Atrial fibrillation / flutter
 Ventricular tachycardia Unknown Other: Specify: _____

E. STROKE

a. If event met CEC criteria for CV event, classify: Non-hemorrhagic Hemorrhagic Unknown

b. Neurological signs / symptoms: Yes No Unknown

c. Abnormal brain imaging study: Yes No Unknown

d. Neurology consultation: Yes No Unknown

e. Other: Specify: _____

F. OTHER CV

a. Non-coronary revascularization: Carotid Abdominal Aorta Renal Femoral Other: Specify: _____

b. Other Cardiac surgery: AVR/ MVR Pacemaker / Defibrillator Implantation Other: Specify: _____

c. Thromboembolic event: Pulmonary embolus Venous thrombophlebitis Other: Specify: _____

d. Cardiac Arrest/Resuscitated Sudden Death

e. Other: Specify: _____

G. CONGESTIVE HEART FAILURE

a. Hospital admission for the management of heart failure.

b. Hospital admission for another reason in which the management of heart failure becomes a major component of hospital stay.

H. RESUSCITATED SUDDEN DEATH

(Sudden Death or Cardiac Arrest successfully resuscitated [consciousness regained] by cardioversion/defibrillation or CPR)

I. MI a. Clinical presentation: _____

b. Cardiac Markers (peak values reported below):

CK value: _____ / ULN: _____ Unknown Not Done

CKMB value: _____ / ULN: _____ Unknown Not Done

Troponin value: _____ / ULN: _____ Unknown Not Done

c. ECG changes: Significant new Q waves (or R waves in V₁ or V₂)

New LBBB

Other: Specify: _____

Unknown

Evolving ST-T wave changes in two contiguous leads

ST elevation

None

J. HOSPITALIZATION FOR UNSTABLE ANGINA

a. Ischemic chest pain/symptoms prompting hospital admission? Yes No

b. Cardiac Markers (peak values reported below):

CK value: _____ / ULN: _____ Unknown Not Done Other: _____

CKMB value: _____ / ULN: _____ Unknown Not Done Other: _____

Troponin value: _____ / ULN: _____ Unknown Not Done Other: _____

c. ECG changes: ≥ 0.5 mm ST depression in two contiguous leads

≥ 1 mm S-T elevation in two contiguous leads

(or S-T depression in V₁ or V₂)

Unknown

≥ 2 mm T wave change in at least two contiguous leads

≥ 0.5 mm ST change compared to most recent or stable trace

Other: Specify: _____

Section III. Composite Events

a. Is there a composite event identified in conjunction with the above reported event ?

No Yes → Specify Event: _____

Composite Event Date: _____

Section IV. Additional Details/Justification:

Comments: _____

Physician Reviewer Signature: _____ Date: ____/____/____

Physician Reviewer Signature: _____ Date: ____/____/____

CEC Administration Signature: _____ Date: ____/____/____

Appendix 6: CTSA Statistical Analysis Plan

**Plan for Prospective Pooling of Data
from Six Studies of Celecoxib:
the Cross-Trial Safety Analysis**

April 10, 2007

Version 4

CONFIDENTIAL

**Janet Wittes, Ph.D.
Statistics Collaborative**

1. Introduction

On December 17, 2004, the NCI-sponsored the Adenoma Prevention with Celecoxib (APC) trial, a prospective, randomized, double-masked, multi-center trial studying the use of celecoxib for the prevention of new adenomatous polyps in patients following polypectomy, stopped active treatment with celecoxib because its Data Safety Monitoring Committee identified higher risk of serious cardiovascular and cerebrovascular events in the active treated groups [Solomon et al.¹] The study was a three-arm trial comparing the efficacy and safety of celecoxib 200 mg bid and celecoxib 400 mg bid versus placebo in reducing the occurrence of newly detected adenomatous polyps in the colorectum at Year 1 and Year 3 after endoscopic polypectomy. On that same day the Pfizer-sponsored Prevention of Spontaneous Adenomatous Polyps (PreSAP) trial, which was comparing the efficacy and safety of celecoxib 400 mg QD to placebo in reducing the occurrence of new adenomatous polyps post-polypectomy in the colorectum at Year 1 and Year 3 of study drug administration, also stopped active treatment although at the time of stopping, the data did not show an increased risk of cardiovascular or cerebrovascular events.

Later that day, the NIA-sponsored ADAPT trial, a randomized multi-center clinical trial comparing naproxen sodium (220 mg bid), celecoxib (200 mg bid), and placebo with respect to prevention of Alzheimer's disease and the attenuation of age-related cognitive decline, suspended further study

CTSA DATA ANALYSIS PLAN

April 10, 2007

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drug. The planned follow-up for the study was several years from the start of enrollment in 2001. The suspension of treatment with celecoxib was in response to the results of the APC trial, rather than because of evidence of increased risk in ADAPT itself. Treatment with naproxen was also suspended because of the ADAPT investigators' reluctance to imply, by continuing, that naproxen was safer than celecoxib when the data from ADAPT did not support this conclusion.

At the same time, the NIH was sponsoring three other long-term trials of celecoxib:

1. The MA27 trial, performed as part of the NCI cooperative group program, is a randomized phase 3 factorial trial comparing two aromatase inhibitors, exemestane (2-5 mg/day) and anastrozole (1 mg/day), with or without celecoxib (200 mg, two capsules twice daily, i.e., 400 mg bid) in postmenopausal women with histologically or cytologically confirmed, receptor-positive, adequately excised, primary breast cancer. Celecoxib and its placebo were double-masked. The trial aimed to compare event-free survival between women treated with exemestane or anastrozole as adjuvant therapy and to determine the effect of adding celecoxib to those therapies. Women were to receive exemestane or anastrozole for five years and celecoxib for three.
2. The Celecoxib Diabetic Macular Edema study (CDME), a 2X2 factorial trial sponsored by the NEI, was designed to compare (1) diode (micropulse) laser photocoagulation to mild Early Treatment Diabetic Retinopathy Study (ETDRS)-style focal photocoagulation and (2) celecoxib (200 mg bid) to placebo for three months prior to and following laser coagulation. Participants in this trial have diabetic retinopathy and clinically significant macular edema. The protocol specified that each participant take celecoxib or its placebo for 36 months after randomization.
3. The Selenium Study (formerly called the Celecoxib/Selenium Study, or Cel/Sel), an NCI-sponsored phase 3 trial, is a factorial study designed to compare (1) celecoxib (400 mg QD) to placebo and (2) selenium (200 µg/day) to placebo on recurrence of adenomatous polyps in persons with adenomatous colon polyps. Participants remain on the intervention stake of the study for three to five years, then are followed for another 5 years after they exit the intervention stage.

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Soon after the announcement by APC, PreSAP, and ADAPT of plans to stop active therapy, these three studies asked their participants to stop taking celecoxib or its placebo.

Specifically,

1. On December 17, 2004, having learned of the decisions made in APC and PreSAP, the study leadership of MA27 sent letters to all investigators asking them to inform their participants to stop celecoxib or its placebo. On December 20, 2004, the Trial Committee met and decided to continue the study with all women remaining on their masked aromatase inhibitor. At the time of this change, the first woman had been on the study for approximately 18 months.
2. On December 20, 2004, the CDME Data Safety Monitoring Committee (DSMC) thoroughly reviewed the accumulating study outcomes and adverse events reported for all the enrolled participants in the CDME study. The DSMC recommended (a) that new enrollment cease, (b) that participants withdraw from the study drug and continue to be followed for another year, and (c) that participants remain masked to two different laser photocoagulation treatments for diabetic retinopathy. On December 22, 2004 the CDME study express mailed letters to all participants instructing them to stop taking their study drug. In addition, the study coordinators made follow-up phone calls to each participant. All study participants will be followed through December 2005.
3. On December 20, 2004, the Selenium Study received official approval from its External Data and Safety Monitoring Board (EDSMB) to discontinue celecoxib audits placebo. The following day, the University of Arizona (UA) Institutional Review Board (IRB) gave approval to notify participants by telephone of their celecoxib arm. The staff at each clinic began contacting all participants to inform them to stop taking the celecoxib-component intervention. The EDSMB and the UA IRB approved a letter that informed participants to stop taking the celecoxib-component study medication. Letters were sent to participants by certified mail on December 23, 2004 and December 28, 2004. Participants who were not notified over the phone of their treatment group were notified at their next clinic visit. Upon approval of the revised protocol and consent form, accrual to the Selenium Study resumed. All necessary study documents (including forms, questionnaires, calendars, and brochures)

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were revised to reflect the change in the study and were sent to the IRB for review and approval.

In the interest of understanding the effect of celecoxib on safety, the NCI has asked the investigators from these six studies to cooperate in summarizing the available long-term data on the risk of cardiovascular and cerebrovascular events among patients taking celecoxib. (Hereafter we refer to cardiovascular and cerebrovascular as "cardio/cerebro-vascular".) This document describes the planned analysis of the combined data from all six studies.

The philosophy governing the planned analyses is based on the belief that because these are randomized studies, the proper analyses should use a true intent-to-treat approach. That is, participants should be classified into the group to which they were randomized and followed for adverse events of interest as long as the protocol specifies even if they stop taking study medication. Further, all analyses should stratify by study.

The analysis will proceed in three steps:

1. Adjudication of events;
2. Analysis of data from each study;
3. A prospective synthesis of the results from all six studies.

2. Classification of events

A "Clinical Endpoint Committee" (CEC) from the Brigham and Women's Hospital (BWH), masked to treatment assignment, classified each death and serious adverse event (SAE) reported through January 6, 2005, from both APC and PreSAP, as cardio/cerebro-vascular or not.

The committee will use the same procedure to classify all deaths and adverse events of interest in each of the remaining four studies through the end of January, 2005. In addition, the committee will classify all deaths or serious adverse events that occurred in APC and PreSAP through January 31, 2005 but not included in the previous classification because of delays in reporting. A Manual of Operations describes the process of evaluation and classification of events. See Section 3.4 for a study-by-study description of the events to be brought to the attention of the CEC.

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Statistics Collaborative will unmask the data and analyze them according to the plan described below.

3. Available data

The analyses will use four types of data: randomization data, baseline data, data on the events to be classified, and data concerning exposure to study drug (celecoxib or its placebo).

3.1. Randomization data

After Statistics Collaborative, Inc. (SCI) has written programs to analyze the data, each study will provide Statistics Collaborative with treatment identifiers for each study participant.

3.2. Baseline data

All studies collected a considerable amount of baseline data. The only baseline data to be used for the prospective pooling will be information related to randomization strata, demographic data, and data directly related to risk of cardiovascular disease. The studies collected information on baseline data differently. The Attachments show the forms used by each study to collect the information.

Each study will have two sets of baseline variables:

- "Native" definitions will be based on the data actually collected in each study.
- CTSA definitions will be derived variables defined to produce uniformity across the six studies.

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The randomization strata are as follows:

Study	Randomization Strata
ADAPT	<ol style="list-style-type: none">1. Field site2. Age category: 70-74; 75-79; 80 +
APC	<ol style="list-style-type: none">1. Center: some randomization "centers" included more than one "site"2. Low dose aspirin: taking or not taking
CDME	The study randomized participants to celecoxib or placebo and then each eligible eye to either diode or mild ETDRS photocoagulation. The analysis or the prospective pooling will use three strata: only diode, only mild ETDRS, or one eye diode and one eye mild ETDRS.
MA27	<ol style="list-style-type: none">1. Aromatase inhibitor: exemestane or anastrozole (part of factorial design)2. Lymph node status at diagnosis: negative; positive; unknown3. Prior adjuvant chemotherapy: yes, no4. Concurrent low dose prophylactic aspirin use < 81 mg/day: yes, No
PreSAP	<ol style="list-style-type: none">1. Country2. Low dose aspirin: taking or not taking
Selenium Study	<ol style="list-style-type: none">1. Selenium: 200 µg/day or placebo (part of factorial design)2. Low dose aspirin: taking or not taking3. Clinical center

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CTSA DATA ANALYSIS PLAN

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The four demographic variables collected age, sex, race, and ethnicity, which are defined as follows. For the purpose of the prospective pooling analysis, race and ethnicity will be combined into one variable.

Demographic variables							
	ADAPT	APC	CDME	MA27	PreSAP	Selemium Study	CTSA
Age	Age of Randomization						
Sex	Male/Female						
Race							
White	W	W	W	W	W	W	W+H
Black/AA	B	B	B	B	B	B	B
Asian/Hawaiian/Pacific Islander							A
Asian		A	A	A	A	A	
Asian/Pacific Islander	A						
Hawaiian/Pacific Islander			A	A		A	
American Indian/Alaska Native	I	I	I	I	I	I	I
Hispanic/Latin American	H	H			H		
Unknown/> 1		U*	U	U	U*	U	U + U*
Ethnicity							
Hispanic			H	H		H	H
Non-Hispanic			N	N		N	All Others
Unknown			K	K		K	K + U*

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The risk factors to be considered are listed below.

Cardio/cerebrovascular risk factors present at randomization						
	APC	ADAPT CDME	MA27	PreSAP	Selenium	CTSA
Cardio/cerebrovascular history	See appendices for native definitions of these risk factors.					x
Hypertension or on antihypertensive medication						x
Diabetes or on diabetes medication						x
Hyperlipidemia or on lipid lowering medication						x
On low-dose aspirin						x
Smoking						x
Current						x
Former						x
Never						x

3.3. Follow-up/censoring

Participants randomized into these studies agreed to be followed for a specific length of time. The following table shows the planned period of treatment in each study. For the prospective pooling analysis, we shall assume that all participants should have been followed through January 31, 2005 for endpoints, including cardio/cerebrovascular adverse events, for the entire planned period of treatment even if they stopped taking study drug. Any participant followed for a shorter period of time will be censored at the date of censoring recorded in the database.

Censoring will be defined by whichever date came first among the following: 1) death; 2) last date of contact (which may be many months later than the last receipt of study medication); 3) date of completed, planned follow-up; or 4) January 31, 2005.

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Study	Protocol-planned follow-up for celecoxib	Censoring for analysis
ADAPT	Up to 7 years	<p>In-person visits occur every 6 months and telephone contacts occur between in-person visits. Thus, participants are contacted approximately every 3 months.</p> <p>For the purpose of the CTSA analysis, data on adverse events of interest will be collected for all participants through the last visit prior to and including January 31, 2005.</p>
APC	Three years after randomization	<p>For participants randomized prior to December 17, 2001: 37 months of follow-up. For participants randomized on December 17, 2001 or later: all events through January 31, 2005.</p>
MA27	Participants agreed to take celecoxib for three years after randomization but were to be followed until the end of the study.	<p>The first participant entered the study in 2002, less than three years before the study stopped its celecoxib arms. Therefore, for all participants, follow-up for adverse events of interest will continue through January 31, 2005 which is 40 days after the study stopped administration of celecoxib or its placebo.</p>
CDME	Three years after randomization	<p>All participants will be followed for adverse events of interest through January 31, 2005.</p>
PreSAP	Three years after randomization	<p>For participants randomized prior to December 17, 2001: 37 months of follow-up. For participants randomized on December 17, 2001 or later: all events through January 31, 2005.</p>
Selenium Study	Three to five years after randomization_ The planned length of follow-up depended on the recommendation by the participant's GI physician for a follow-up colonoscopy.	<p>Recruitment began in November 2001 and continued until December 2004 for all four arms of the study. No one had finished follow-up at the time that the study stopped celecoxib. Events will be collected through January 31, 2005. Recruitment continued after December 2004 but only to the selenium and selenium-placebo arms.</p>

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3.4. Deaths and adverse events of interest

The CTSA aims to assess the relationship of use of celecoxib to the occurrence of clinically important cardio/cerebrovascular events. All potential cardio/cerebrovascular serious adverse events will be identified and then sent to the Clinical Events Committee (CEC) for classification. For the process of classification, see the Manual of Operations of the CEC.

The six studies collected data on these events somewhat differently. APC, CDME, MA27, and PreSAP defined an SAE as an event leading to hospitalization, prolongation of hospitalization, or death, or as an event that is life-threatening. The Selenium Study also considered cancer an SAE. For these five studies, an adverse event need not be attributed to study drug to be called serious.

In ADAPT, the investigators used an FDA definition of reportable serious adverse events to define serious adverse events. A reportable serious adverse event in ADAPT is a serious adverse event that the investigator considers related to study drug. The fact that events termed "serious" in ADAPT are also "related" filters out many cardio/cerebrovascular events. Therefore, for ADAPT an alternative definition of serious adverse events has been adopted for the CTSA. ADAPT classified every event according to the NCI's Common Toxicity Grades. For ADAPT, all Grade 3 and 4 events, as well as all potentially relevant events recorded at regular contacts (e.g., MIs, strokes, and hospitalizations) will be defined as potential "events of interest" to be considered candidates for review by the "BWH classification team. This set of events is nearly the same as the set of serious adverse events defined by the other five studies.

We recognize that the two sets of definitions — serious adverse events in all but ADAPT and Grades 3 and 4 events plus "serious adverse events" in the other three studies — differ somewhat. We considered expanding the definition of events of interest to Grade 3 and 4 non-serious adverse events in all studies to make the definitions across studies more apparently uniform but decided against doing so because Grade 3 and 4 non-serious adverse events in these three studies are unlikely to include myocardial infarctions, stroke, pulmonary embolism, or severe heart failure. Moreover, in these three studies, the investigators do not collect supporting information for nonserious adverse events; thus a Grade 3 or 4 non-serious cardio/cerebrovascular event will be very difficult to classify. For APC and PreSAP, Pfizer reviewed all Grade 3 and 4 every to make

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certain they did not fulfill the definition of "serious." If on review Pfizer determined that an event the investigator classified as non-serious met the definition for serious, the investigator was asked to review and reclassify the event as appropriate. This process assured that all SAEs will come to the attention of the CEC.

Because some of the events in ADAPT lack supportive documentation, the Clinical Evaluation Committee has classified the events as "definite", "probable", and "uncertain". The supportive documentation in the category "definite" corresponds most closely to the documentation in the other studies; therefore, the primary analysis of data from ADAPT will use the "definite" events.

The fact that the definitions are not consistent across studies adds strength to the statistical necessity of analyzing the data stratified by study. As long as the probability that an event identified within a trial is independent of the treatment group (celecoxib or placebo), the statistical analysis will remain valid.

3.5. Outcomes

The primary analysis will categorize composite outcomes hierarchically: An event is added to the hierarchy in a way that reflects increasing subjectivity of diagnosis and, presumably, less likelihood of being affected by celecoxib. Note that all endpoints include all deaths from any cardiovascular or cerebrovascular cause; the endpoints differ from each other according to the non-fatal events included. By definition, the number of events increases as we move down the hierarchy. By structure, all the composite endpoints are correlated with each other. If there is truly an effect of celecoxib on the most objectively defined of these events, we would expect the estimated hazard ratio to tend to decrease as we move down the hierarchy but we would anticipate that the p-values would likely first decrease as the number of events increases and then increase as the hazard ratios decrease. Because there is no a priori reason to assign myocardial infarction (MI) and stroke a position in this hierarchy, we will consider them at the same level. The last outcome in the list, "Other cardiovascular event" is not part of the hierarchy because it excludes the events above it. We expect the hazard ratio for that event to be close to 1. Note the hierarchy below differs somewhat from the hierarchy used in APC and PreSAP because the prespecified endpoints for the APC and PreSAP trials did not include venous thromboembolism.

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- Death from cardio/cerebrovascular causes
- Death from cardio/cerebrovascular causes or non-fatal MI
- Death from cardio/cerebrovascular causes or non-fatal MI or stroke
- Death from cardio/cerebrovascular causes or non-fatal MI or stroke or venous thromboembolism (pulmonary embolism or deep vein thrombosis)
- Death from cardio/cerebrovascular causes or non-fatal MI or stroke or venous thromboembolism or heart failure
- Death from cardio/cerebrovascular causes or non-fatal MI or stroke or venous thromboembolism or heart failure or angina
- Death from cardio/cerebrovascular causes or non-fatal MI or stroke or venous thromboembolism or heart failure or angina or need for a cardiovascular procedure
- Other cardio/cerebrovascular event. The Manual of Operations for the CEC defines "other cardio/cerebrovascular event".

We will also consider the endpoint Death from cardio/cerebrovascular causes or non-fatal stroke which shares a position equivalent to Death from cardio/cerebrovascular causes or non-fatal MI in the above hierarchy.

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4. Study-specific analyses

The primary treatment groups and the analysis strata for the studies are listed below. Note that ADAPT, APC, and the Selenium Study randomize within clinical center or field site. We are not using these centers as strata for analysis because they are likely to be very small.

Study	Treatment groups	Analysis strata
ADAPT	Celecoxib (200 mg bid) Placebo	Age category: 70-74; 75-79; 80 +
APC	Celecoxib (200 mg bid) Celecoxib (400 mg bid) Placebo	Low dose aspirin: taking or not taking
CDME	Celecoxib (200 mg bid) Placebo	Photocoagulation: only diode: only mild ETDRS; one eye diode and one eye mild ETDRS
MA27	Celecoxib (400 mg bid) Placebo	Aromatase inhibitor: exemestane or anastrozole Lymph node status at diagnosis: negative; positive; unknown Prior adjuvant chemotherapy: yes, no Concurrent low dose prophylactic aspirin use < 81 mg/day: yes, no
PreSAP	Celecoxib (400 mg QD) Placebo	Country Low dose aspirin: taking or not taking
Selenium Study	Celecoxib (400 mg QD) Placebo	Selenium: 200 µg/day or placebo Low dose aspirin: taking or not taking

- For each event or category of event, the following analyses will be performed for each study separately. A table will summarize the distribution of "native" baseline variables and CTSA baseline variables by treatment group.
- Graphical timelines will show the time of occurrence of each event by treatment group. For the composite endpoint "death from cardio/cerebrovascular causes or non-fatal MI or stroke or venous thromboembolism or heart failure", smoothed empirical hazard curves will be constructed for the celecoxib and control groups. If these curves are convincingly nonparallel, we will reassess the appropriateness of the Cox model.
- A table will present the incidence of each event listed in Section 3.4 and the rate per 1,000 patient years treatment group.
- For the events in Section 3.5, a table will present the hazard ratio, calculated from Cox models with the analysis strata, of each celecoxib dose group relative to the placebo

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group along with the standard error of the hazard ratio and its 95 percent confidence interval. We will use maximum likelihood methods to calculate the log hazard ratio, which is approximately normally distributed, and its standard error. We will use Proc PHREG in SAS v. 9 to perform the calculations with the Efron method of handling ties².

- The summary table will include raw attributable risk per 1000 patient years.
- Kaplan-Meier curves will depict the time of occurrence of each event in Section 3.5 for each treatment group.
- For both the "native" and the CTSA baseline variables, a table will summarize subgroup-specific hazard ratios for the incidence of the composite endpoint: death from cardio/cerebrovascular causes, myocardial infarction, stroke, or heart failure along with a test of interaction to see if the effect of celecoxib varies by baseline subgroup. The models will include as variables the analysis strata listed in the table at the beginning of this section.
- Calculations will be performed to examine the power of each study to detect 1.2-fold, 1.5-fold, two-fold, and three-fold increases of risk
- Graphs or tables will summarize the attributable risk as a function of baseline risk.

5. Statistical methods

The goal of the CTSA is to summarize data on the cardio/cerebrovascular events in six specific randomized clinical trials. Our statistical approaches will be those used in meta-analysis, but we are not gathering information from all randomized trials of celecoxib.

One of the strengths of the CTSA is its partially prospective nature. At the time the CTSA was planned, only APC and PreSAP had presented unmasked data to the public.

In selecting these six studies, the NCI used the following criteria:

1. The study had to be randomized, placebo-controlled, and double-masked with respect to celecoxib.
2. The planned follow-up had to be at least three years.

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3. The study had to be large enough to expect enough cardio/cerebrovascular events to permit meaningful analysis.
4. The study had to be funded by the NIH or designed in a way that closely matched the design of an NIH study. The only trial in the latter category was PreSAP.

As of the writing of this plan, the CEC has not yet classified the events from the other studies. Until this plan is complete and approved, no one will have access to the unmasked data classified by the CEC from any of the studies except APC and PreSAP.

Fixed effects and random effects models are the two major statistical approaches used in meta-analysis. Fixed effects models make an underlying assumption of a general, common treatment effect among the studies included. The results from the various studies provide an estimate of that single effect. The random effects approach assumes a normal distribution of treatment effects, with the results from the various studies providing an estimate of the mean effect across a population of potential studies. Bailey³ presents a useful discussion of the advantages and disadvantages of the two approaches. Follman and Proschan⁴ argue that neither approach answers the question people are usually asking. The fixed effect model fails because the assumption of a constant effect size is unlikely to be true and the random effect model fails because it makes a strong, untestable, assumption about the normality of the distribution of the effect of the treatment. They propose instead a randomization test with the sample space defined by the studies in a meta-analysis. There are too few studies in the CTSA to use this approach.

For this analysis of cardio/cerebrovascular outcomes, we shall assume a fixed effects model. We will be asking the narrow question, "What is the best summary measurement of the strength of the relationship between celecoxib use and cardio/cerebrovascular events within the six studies included?" We are not attempting to ask the broader question of the effect of celecoxib in the population of all studies or of all potential studies. The prospective nature of the analysis and the focused question being asked remove one frequent criticism leveled against meta-analyses: that their results are biased because many studies that have not shown expected findings remain unpublished (the "file-drawer problem"). See Pater, et al. for a description of this type of pre-planned pooling in another context⁵.

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5.1. Pooled analysis of the hazard ratio

The primary approach to the analysis will be to calculate the hazard ratio for each study using a stratified Cox regression model. For ADAPT, as described above, we will use the events classified as "definite" by the CEC. For the APC study, we will calculate the hazard ratio for the combined high and low dose groups. Thus, we will have six estimated hazard ratios, one for each study. For the fixed-effects pooled analysis, we will calculate each log hazard ratio, which is approximately normally distributed. The average of these log hazard ratios, weighted by the inverse of their variances, will provide an estimate of the pooled log hazard ratio. Exponentiating this pooled value will produce the estimated hazard ratio that summarizes the results across the six studies. This first analysis will ignore the fact that the doses differ in the various studies.

More formally, let h_1, h_2, \dots, h_6 represent the six log hazard ratios. Let W_i represent the inverse of the i 'th variance of the estimated log hazard ratio, that is, $1/\text{Var}(h_i)$. Then, the mean of the log hazard ratios is:

$$H = \sum w_i h_i / \sum w_i \quad (i=1, 2, \dots, 6)$$

with variance $V = (\sum w_i)^{-1}$.

Under the null hypothesis that the pooled log hazard ratio is equal to 0, the quantity $t = H/V^{1/2}$ is approximately normally distributed with mean 0 and variance 1. The two-sided standardized test statistic t will be used to test the null hypothesis with a Type I error rate of 0.05. The quantity $\exp(H)$ provides a point estimate of the common hazard ratio across the six studies. The estimated 95 percent confidence interval is $\exp(H \pm 1.96 V^{1/2})$.

The estimated log hazard ratio H has an upward bias because the APC study stopped in response to an observed increase in cardio/cerebrovascular events. Jennison and Turnbull⁶ and Proschan, Lan, and Wittes⁷ describe methods of adjusting for this upward bias in the context of planned interim analyses. Because the APC trial had no a priori plan to stop the study in response to an excess of cardio/cerebrovascular events, there is no technically unambiguous way to make the correction. For exploratory purposes, we will assume that if APC had had an a priori stopping rule for cardio/cerebrovascular safety, that rule would have been based on either an O'Brien-Fleming or a Pocock boundary with either a one-sided 0.05 or a one-sided 0.10 level for safety. We will further

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assume that the study would have had only a single formal interim look for safety. We will then calculate the "pull-back" estimators under these four assumptions (two classes of boundaries -O'Brien-Fleming and Pocock - times two type I error rates - 0.05 and 0.10) and incorporate them into the pooled hazard ratio. These four new estimates will provide insight into the robustness of the estimated hazard ratio described in the previous paragraph.

5.2. Reliability of the adjudication

Two physicians adjudicate each event. A physician experienced in adjudicating cardiovascular events, is the first adjudicator. A cardiologist reviews each event; for cases where the two physicians disagree, they reach consensus on categorization. The decision from this pair of physicians is termed the "primary adjudication".

The following- procedure will be implemented to assess the reliability of the process and hence the robustness of the statistical results. An "event" here is defined as any event that went to the adjudication team, whether or not the adjudicators judged it as cardiovascular.

- For the four studies whose events have not yet been adjudicated (ADAPT, CDME, MA27, and The Selenium Study), a second cardiologist will independently review:
 - each event about which the two adjudicators do not come to consensus
 - a 10 percent sample of all events about which the two adjudicators agree

These two sets of events will be presented in a blinded manner so that the second cardiologist is not aware of whether the event represent one for which the two primary adjudicators agreed or disagreed.

To maintain consistency with APC and PreSAP, the consensus categorization of the two primary adjudicators will be used for the statistical analysis.

- The second cardiologist will review a 10 percent scruple of all APC and PreSAP events. Tables will display the degree of concordance of the primary and secondary adjudication with respect to:

- Agreement on whether the event was cardiovascular or not

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- If cardiovascular, agreement on the particular diagnosis

The robustness of the results of the study will be assessed in relation to the observed degree of concordance.

Tables will show the results if the endpoints from ADAPT include the "probable" events and if they also include the "possible" events.

5.3. Mantel-Haenszel pooled odds ratio

Most meta-analyses of binary data produce a pooled odds ratio through a modified Mantel-Haenszel test (see, for example, Hedges and Olkin⁸). Most of the examples we have seen in the medical literature ignore the randomization strata of the original studies. We have chosen to use Cox models because they allow a natural way to adjust for different follow-up time in the six studies and to stratify by randomization variables. We will calculate the ordinary Mantel-Haenszel pooled odds ratio to show the conclusions that would have been made had we used the usual method. If the two estimates - a pooled hazard ratio from the Cox models and a pooled odds ratio from the Mantel-Haenszel test - yield materially different answers, we will explore the reasons for the discrepancy.

5.4. A Bayesian analysis

Smith et al.⁹ describe methods for Bayesian random effects meta-analysis. In an unpublished manuscript, Kaizar et al.¹⁰ describe a Bayesian meta-analysis that can incorporate strata in which no event occurs. We will use the methods of those papers to provide a Bayesian estimate of the pooled hazard ratio. We will use a flat (that is, a so-called "non-informative") prior with a mean of zero for the log hazard ratio.

In addition, for exploratory purposes, we will calculate the hazard ratio under a diffuse prior setting the mean at the estimated hazard ratio reported in the APPROVe trial.

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6. Effect of dose

An important question to address is the effect of dose. Therefore, three dose-specific meta-analyses will be performed:

- 400 mg bid: APC (high dose) and MA27
- 200 mg bid: ADAPT, APC (low dose), and CDME
- 400 mg QD: PreSAP and the Selenium Study

Some biological arguments suggest that if celecoxib has adverse cardio/cerebrovascular effects, the 400 mg bid dose should have the largest effect, the 200 mg bid dose the next largest, and the 400 mg QD dose the smallest. One model will include all three dose regimens, stratified by study, and test the dose response.

7. Effect of baseline risk

In their papers on the APC and PreSAP studies, Solomon et al.¹ and Arber et al.¹¹ examine whether the hazard ratio of celecoxib use is related to baseline risk of cardiovascular disease. In neither case is the interaction between any baseline risk factor and hazard ratio statistically significant; on the other hand, in both papers, the data are consistent with an increased hazard ratio for those with higher baseline risk. The CTSA allows an opportunity to explore these relationships with a larger sample size. For each baseline variable listed in Section 3.1, a Cox model will be constructed with a term for main effect of the variable and an interaction between that variable and the main effect of celecoxib.

In addition, a simple four-category risk factor variable will be created:

- Low: No known risk factor
- Moderately low: Men >55 years of age; women >65 years of age; no other known risk factor
- Moderate: One of the following: age >75; hypertension or on antihypertensive medication; hyperlipidemia or on lipid-lowering medication; current smoker; on low-dose aspirin

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- High: Diabetes, prior history of cardiovascular disease, or any two risk factors in the "moderate" list.

A Cox model, stratified by study but with all treatment groups combined, will be constructed to confirm that the ratios of successive hazard ratios in this four category list are at least 1.5. If they are not, we will modify the categories to create a risk factor variable with that property. We will use this variable in a pooled analysis with a four-level graded interaction term to gain a better understanding of the relationship between cardio/cerebrovascular risk and use of celecoxib.

8. Analyses by time on study drug

We plan to take an intent-to-treat approach in the analyses — the analysis will include all subjects in the group to which they were randomized and follow-up for cardio/cerebrovascular events will continue as long as the subject does not withdraw from the study. We recognize that this approach is somewhat controversial many people believe that analyses of safety should only include events that occur within a short time after cessation of study medication. For example, Bresalier et al.¹² followed patients only for 14 days after they stopped study medication. Other investigators use 30 days as the cut-off. We believe that in trials the data rarely capture with precision the date a participant has stopped study medication. Moreover, we take the position that we cannot presume to know why a participant in a trial stopped study medication and therefore whether a delayed event was or was not related to the study medication. This approach, by including a long period of time after cessation of study medication, may dilute the effect. We will perform exploratory analyses using various assumptions concerning time on study medication if the data are sufficiently complete to make such analyses interpretable.

Acknowledgements

Representatives from all the studies contributed helpful information on their own trials. Jonghyeon Kim, Joe Pater, and Rebecca Rosenstein provided useful contributions to the statistical methodology in this plan. Gretchen Arndt collected relevant information from the studies. Both she and Stefanie Obara edited this document.

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Attachment A. Baseline demographic and cardiovascular variables

ADAPT

19. Use of 4 or more doses per week of either of the following in the 14 days prior to enrollment:

- Non-aspirin NSAIDs (any dose) or aspirin (>81 mg per day)
- Histamine H2 receptor antagonists

Yes (1) No (2)

Participants taking 4 or more doses of aspirin per week (e.g., for cardiac prophylaxis) are eligible if they are willing to limit use to <81 mg per day.

C. Current medication use

For items 30-42, ask participant about all listed medications. If additional other specify lines are needed, record in item 43.

30. Is the participant currently taking any non-steroidal anti-inflammatory, pain relieving, or aspirin-containing medications (check all that apply)

- a. Acetaminophen (Tylenol[®]): (1)
- b. Aspirin - 325 mg: (1)
- c. Aspirin - 81 mg: (1)
- d. Celecoxib (Celebrex[®]): (1)
- e. Ibuprofen (Advil[®], Motrin[®]): (1)
- f. Indomethacin (Indocin[®]): (1)
- g. Naproxen (Aleve[®]): (1)
- h. Rofecoxib (Vioxx[®]): (1)
- i. Valdecoxib (Bextra[®]): (1)
- j. Other (specify): (1)

_____ specify

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19. Cigarette smoking:

a. Has the participant ever smoked cigarettes
 (Yes) (No)
 () ()
 20.

("No" means less than 20 packs of cigarettes or 12 ounces of tobacco in a lifetime or less than 1 cigarette a day for one year)

b. Age when first started cigarette smoking

 years

c. Age when last stopped smoking cigarettes or current age if currently smoking

 years

d. On the average for the entire time smoked, number of cigarettes smoked per day

 # cigarettes per day

e. Currently smoke cigarettes
 (Yes) (No)
 () ()
 20.

f. Current number of cigarettes smoked per day

 # cigarettes

20. Cigar smoking:

a. Has the participant ever smoked cigars
 (Yes) (No)
 () ()
 21.

b. Does the participant currently smoke cigars
 (Yes) (No)
 () ()

21. Tobacco pipe:

a. Has the participant ever smoked a tobacco pipe
 (Yes) (No)
 () ()
 22.

b. Does the participant currently smoke a tobacco pipe
 (Yes) (No)
 () ()

C. Medical history related to eligibility

22. Peptic ulcers:

a. Has the participant ever been diagnosed with a peptic ulcer
 (Yes) (No)
 () ()
 22a.

b. Has the participant ever had a peptic ulcer complicated by perforation, hemorrhage or obstruction
 (Yes) (No)
 () ()
 22b.

c. Has the participant had any signs or symptoms suggestive of an ulcer within the past 28 days
 (Yes) (No)
 () ()
 23.

C If Yes, the participant cannot be scheduled for an enrollment visit until asymptomatic for at least 28 days.

d. Date when last had symptoms

 day month year

23. Treatment for hypertension (check all that apply):

a. Never treated ()
 b. Treated in the past ()
 c. Currently treated ()

24. Has the participant ever been diagnosed with (check all that apply):

a. Infectious hepatitis ()
 b. Cirrhosis ()
 c. Obstructive jaundice ()
 d. Other liver disease (specify) ()

_____ specify

e. None of the above ()

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25. Has the participant ever been diagnosed with (check all that apply):
- a. Kidney or ureter stones ()
 - b. Renal insufficiency ()
 - c. Other kidney disease (specify) ()
- _____ specify _____
- d. None of the above ()

26. Hypertension/anemia:
- a. Does the participant have hypertension or anemia sufficient to disqualify her/him from enrollment

Yes No
 27.

If Yes, specify: _____
 specify

C If Yes, the participant cannot be scheduled for an enrollment visit until the condition is controlled. (Refer to guidelines provided in ADAPT Handbook.)

- b. Date (within 42-day eligibility window) when participant was determined to no longer have hypertension or anemia sufficient to preclude enrollment
- _____ day _____ month _____ year

27. Does the participant have liver disease or kidney disease sufficient to disqualify her/him from enrollment:
- Yes No
 STOP
- If Yes, specify: _____
 specify

D. General medical history

28. Strokes:
- a. Has participant ever had a stroke
- Yes No
 29.
- b. How many strokes has the participant ever had
- _____ # strokes
- c. Year of last stroke _____ year

29. Has the participant ever had a transient ischemic attack (TIA):
- Yes No

30. Has the participant ever had a head injury that caused loss of consciousness or amnesia lasting for one hour or more:
- Yes No

31. Has the participant ever had any of the following (check all that apply):
- a. Brain surgery ()
 - b. Penetrating brain injury ()
 - c. Depressed skull fracture ()
 - d. Coronary artery bypass surgery ()
 - e. None of the above ()

32. Has the participant ever been diagnosed with (check all that apply):
- a. Cancer other than non-melanoma skin cancer ()

 specify
 - b. Clinical depression or other psychiatric illness (specify) ()

 specify
 - c. Angina, which lasted half an hour or more ()
 - d. Congestive heart disease or failure ... ()
 - e. Myocardial infarction (MI) (specify year of most recent MI) ()

 year
 - f. Emphysema or chronic obstructive pulmonary disease ()
 - g. Asthma ()
 - h. Epilepsy (specify year of most recent seizure) ()

 year
 - i. Parkinson's disease ()
 - j. Other neurodegenerative disease (specify) ()

 specify
 - k. Osteoarthritis ()
 - l. Rheumatoid arthritis ()
 - m. Atrial fibrillation ()
 - n. Cataracts ()
 - o. Diverticulitis ()
 - p. Polyps ()
 - q. Autoimmune disorder (specify) ()

 specify

- r. Other diagnosis (specify) ()

 specify
- s. Other diagnosis (specify) ()

 specify
- t. Other diagnosis (specify) ()

 specify
- u. None of the above ()

33. Treatment for hyperlipidemia (check all that apply):
- a. Never treated ()
 - b. Treated in the past ()
 - c. Currently treated ()
34. Treatment for diabetes (check all that apply):
- a. Never treated ()
 - b. Treated in the past ()
 - c. Currently treated ()

35. Hospitalizations:
- a. In the past year, has the participant been hospitalized
 Yes () No ()
 36.
 - b. Number of hospitalizations _____
 # hospitalizations
 - c. Total number of days _____
 # days

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37. Sustained use of medications:

a. Has the participant used 4 or more doses per week of either of the following within the past 14 days

- Non-aspirin NSAIDs (any dose) or aspirin (> 81 mg per day)
- Histamine H2 receptor antagonists

^(Yes 1)
C

^(No 2)
38.

b. Date of most recent sustained use

____ day ____ month ____ year

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APC

Patient subgroups will be identified according to the presence or absence of selected medical history terms and related information in records of screening or baseline clinic visits as follows (the absence of medical history terms does not confirm the absence of the respective risk factors in particular patients):

- Hypertension, including verbatim terms that correspond to International Classification of Diseases (ICD-9) codes for essential hypertension (401.x), hypertensive heart disease (402.x), hypertensive renal disease (403.x), hypertensive heart and renal disease (404.x), and secondary hypertension (405.x). Additional patients with risk factors in this category will be identified as indicated in records of screening or baseline clinic visits using check boxes (no/yes, history [not currently]/yes, currently has) for hypertension.
- Atherosclerotic heart disease, including verbatim terms that correspond to ICD-9 codes for acute myocardial infarction (410.x), other acute and subacute forms of ischemic heart disease (411.x), old myocardial infarction (412.x), angina pectoris (413.x), other forms of chronic ischemic heart disease (414.x), atherosclerotic cardiovascular disease (429.2), operations of vessels of heart (Procedure Code 36.x, including percutaneous transluminal coronary angioplasty), and carotid endarterectomy (Procedure Code 38.12). Additional patients with risk factors in this category will be identified as indicated in records of screening or baseline clinic visits using check boxes (no/yes, history [not currently]/yes, currently has) for atherosclerotic cardiovascular disease, angina, and myocardial infarction.
- Cerebrovascular disease, including verbatim terms that correspond to ICD-9 codes for carotid artery occlusion (433.x), cerebral thrombosis and cerebral artery occlusion (434.x), transient cerebral ischemia (435.9), cerebrovascular accident (436), cerebrovascular disease (437.x). Additional patients with risk factors in this category will be identified as indicated in records of screening or baseline clinic visits using check boxes (no/yes, history [not currently]/yes, currently has) for cerebrovascular ischemia and as indicated in records of screening or baseline clinic visits using check boxes (no/yes, history [not currently]/yes, currently has) for cerebrovascular ischemia.
- Diabetes, including verbatim terms that correspond to ICD-9 codes for diabetes mellitus (250.x) and diabetic neuropathy (357.2). Additional patients in the APC trial with risk factors in this category will be identified as indicated in records of screening or baseline clinic visits using check boxes (no/yes, history, [not currently]/yes, currently has) for insulin-dependent diabetes, diet-controlled non-insulin dependent diabetes (NIDDM), medication-controlled NIDDM, and otherwise-controlled NIDDM.
- Hyperlipidemia, including verbatim terms that correspond to ICD-9 codes for disorders of lipid metabolism (272.x). Additional patients in the APC trial with risk factors in this category will be identified as indicated in records of screening or baseline clinic visits using check boxes (no/yes) for the following question: "Is the subject using cholesterol-reducing medication?"

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- Smoking, determined as indicated by check box in records of screening or baseline clinic visits (smoker = checked box for either "current smoker" or "former smoker," and nonsmoker = checked box for "never smoked"; other tobacco use not considered).

The checkboxes referred to in the above description are shown below.

MEDICAL HISTORY (PART 1 OF 3)

Date of Birth: Gender: Male Female

Race / Ethnic Origin:

Caucasian Black Asian Native American Hispanic / Latin American Other specify: _____

If "YES," specify finding or diagnosis and date (if known).

NO YES

Cardiovascular:

(excluding categories below)

(check one box only)

	No	Yes, history (not currently)	Yes, currently has
Angina	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Hypertension	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Congestive Heart Failure	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Atherosclerotic Cardiovascular Disease	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Myocardial Infarction	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Peripheral Edema	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Cerebrovascular Ischemia (TIA +/- CVA)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Endocrine:

(excluding categories below)

(check one box only)

	No	Yes, history (not currently)	Yes, currently has
Insulin dependent diabetes	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Diet controlled NIDDM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Medication controlled NIDDM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Otherwise controlled NIDDM	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

If "YES," specify finding or diagnosis and date (if known).

NO YES

Cancer:

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MEDICATION:

Is the subject using low dose aspirin ($\leq 325\text{mg}/\text{QOD}$ or $\leq 162\text{mg}/\text{QD}$) NO YES

Is the subject using cholesterol-reducing medication?

Does the subject have a previous history of chronic NSAID/analgesic use?

If "YES", total duration:

--	--	--	--

(Please remember to record current medications on Baseline medications CRF)

TOBACCO USE:

Cigarette History (choose one):

Never smoked:

Current smoker: Number of cigarettes per day:

--	--

 Number of years smoked:

--	--

Former smoker: Date quit smoking:

--	--	--	--	--	--

Other Tobacco Use History (choose one):

Never used:

Current user: Number of years used:

--	--

Former user: Date quit:

--	--	--	--	--	--

Type of Other Tobacco used per day:

Pipe: <input type="checkbox"/>	Pouches: <table style="display: inline-table; border-collapse: collapse;"><tr><td style="border: 1px solid black; width: 20px; height: 15px;"></td><td style="border: 1px solid black; width: 20px; height: 15px;"></td></tr></table>		
Cigar: <input type="checkbox"/>	Each: <table style="display: inline-table; border-collapse: collapse;"><tr><td style="border: 1px solid black; width: 20px; height: 15px;"></td><td style="border: 1px solid black; width: 20px; height: 15px;"></td></tr></table>		
Chew: <input type="checkbox"/>	Pouches: <table style="display: inline-table; border-collapse: collapse;"><tr><td style="border: 1px solid black; width: 20px; height: 15px;"></td><td style="border: 1px solid black; width: 20px; height: 15px;"></td></tr></table>		
Snuff: <input type="checkbox"/>	Cans: <table style="display: inline-table; border-collapse: collapse;"><tr><td style="border: 1px solid black; width: 20px; height: 15px;"></td><td style="border: 1px solid black; width: 20px; height: 15px;"></td></tr></table>		

BASELINE - MEDICATIONS

MEDICATION: List ALL medication(s) subject is currently taking up until first dose of randomized study drug, except NSAIDs, which are to be listed on CRF 33.01.

If none, check here:

Drug Name	Dose/Regimen	Reason For Therapy* (Diagnosis)	Date Started	Date Stopped	Continuing Yes						
			Day Month Year	Day Month Year							
_____	_____	_____	<table style="display: inline-table; border-collapse: collapse;"><tr><td style="border: 1px solid black; width: 20px; height: 15px;"></td><td style="border: 1px solid black; width: 20px; height: 15px;"></td><td style="border: 1px solid black; width: 20px; height: 15px;"></td></tr></table>				<table style="display: inline-table; border-collapse: collapse;"><tr><td style="border: 1px solid black; width: 20px; height: 15px;"></td><td style="border: 1px solid black; width: 20px; height: 15px;"></td><td style="border: 1px solid black; width: 20px; height: 15px;"></td></tr></table>				<input type="checkbox"/>
_____	_____	_____	<table style="display: inline-table; border-collapse: collapse;"><tr><td style="border: 1px solid black; width: 20px; height: 15px;"></td><td style="border: 1px solid black; width: 20px; height: 15px;"></td><td style="border: 1px solid black; width: 20px; height: 15px;"></td></tr></table>				<table style="display: inline-table; border-collapse: collapse;"><tr><td style="border: 1px solid black; width: 20px; height: 15px;"></td><td style="border: 1px solid black; width: 20px; height: 15px;"></td><td style="border: 1px solid black; width: 20px; height: 15px;"></td></tr></table>				<input type="checkbox"/>

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MA-27

PATIENT INFORMATION	
Patient Study ID: _____ <i>(NCIC CTG Patient Serial Number)</i>	Patient Initials: _____ <i>(first - middle - last)</i>
Patient Medical Record Number: _____	Investigator First Name: _____
Institution Name: _____	Investigator Last Name: _____
NCI Institution Number: _____ <i>(CTEP assigned - U.S. sites only)</i>	Registered Investigator: _____ <i>(NCI Investigator Number - U.S. sites only)</i>
Patient's Date of Birth: ____-____-____ <i>yyyy mmm dd</i>	Patient Gender: <input type="checkbox"/> Male <input type="checkbox"/> Female
Patient Race <i>(check ✓ all that apply)</i> <input type="checkbox"/> White <input type="checkbox"/> American Indian or Alaska Native <input type="checkbox"/> Black or African American <input type="checkbox"/> Unknown <input type="checkbox"/> Native Hawaiian or other Pacific Islander <input type="checkbox"/> Asian <i>Patient is encouraged to self designate:</i>	Patient Ethnicity <i>(check ✓ one only)</i> <input type="checkbox"/> Hispanic or Latino <input type="checkbox"/> Non-Hispanic <input type="checkbox"/> Unknown
Race Categories and Definitions: White - A person having origins in any of the original peoples of Europe, Middle East, or North Africa. Black or African American - A person having origins in any of the black racial groups of Africa. Terms such as " Haitian" or "Negro" can be used in addition to "Black or African American" Native Hawaiian or Other Pacific Islander - A person having origins in any of the original peoples of Hawaii, Guam, Samoa and other Pacific Islands. Asian - A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent. Including for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand and Vietnam. American Indian or Alaska Native - A person having origins in any of the original peoples of North, Central or South America, and who maintains tribal affiliations or community attachment	Ethnicity Categories and Definitions: Hispanic or Latino - A person of Mexican, Puerto Rican, Cuban, Central or South American or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino" Non-Hispanic - A person who is NOT Hispanic or Latino

Cardiovascular Morbidity			
Has the patient suffered cardiovascular disease? <input type="checkbox"/> No <input type="checkbox"/> Yes			
Cardiovascular Event	Check (✓)		
	No	Yes	Unknown
Myocardial infarction			
Stroke/transient ischemic attack (TIA)			
On-going angina (no surgical intervention)			
Angina requiring percutaneous transluminal coronary angioplasty (PTCA)			
Thromboembolic event			
Other (specify)* _____			
If other specified, please describe event: _____			
* Report non-ischemic events in the "other" category (e.g. hypertension).			

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3. DISEASE HISTORY / PRIOR TREATMENT / ADVERSE EVENTS	
First Positive Biopsy Date:	_____ - _____ - ____ (date of initial pathologic diagnosis) <small>yyyy mmm dd</small>
Date of Most Extensive Primary Surgery:	_____ - _____ - ____ (Date upon which last diseased tissue - <small>(if required, use last re-excision date) yyyy mmm dd</small> <i>invasive or in situ carcinoma - was removed</i>)
Most extensive primary surgery:	<input type="checkbox"/> partial mastectomy/lumpectomy/excisional biopsy <input type="checkbox"/> mastectomy, NOS
Was sentinel node sampling performed?	<input type="checkbox"/> No <input type="checkbox"/> Yes → if yes, provide the following: <small>(if positive, axillary dissection must be done)</small> Sentinel Node Biopsy Date: _____ - _____ - ____ <small>yyyy mmm dd</small>
Was axillary dissection performed?	<input type="checkbox"/> No <input type="checkbox"/> Yes → if yes, provide the following: Axillary Dissection Date: _____ - _____ - ____ <small>yyyy mmm dd</small>
Number of lymph nodes examined:	_____ <small>(Please complete if either both sentinel node biopsy and/or</small>
Number of positive lymph nodes:	_____ <small>axillary dissection were done.)</small>

PRIOR TREATMENT FOR CANCER: Has the patient received any of the following?		
Prior adjuvant chemotherapy? <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Unknown		
Agent Name <small>(List each agent separately)</small>	Date Prior Adjuvant Chemotherapy Ended <small>(yyyy-mm-dd)</small>	Total Number of Cycles Given
_____	_____ - _____ - ____	
_____	_____ - _____ - ____	
_____	_____ - _____ - ____	
_____	_____ - _____ - ____	
_____	_____ - _____ - ____	

Cardiovascular Morbidity			
Has the patient suffered cardiovascular disease? <input type="checkbox"/> No <input type="checkbox"/> Yes			
Cardiovascular Event	Check (✓)		
	No	Yes	Unknown
Myocardial infarction			
Stroke/transient ischemic attack (TIA)			
On-going angina (no surgical intervention)			
Angina requiring percutaneous transluminal coronary angioplasty (PTCA)			
Thromboembolic event			
Other (specify)* _____			
If other specified, please describe event: _____			

* Report non-ischemic events in the "other" category (e.g. hypertension).

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5. CONCOMITANT MEDICATIONS							
Is the patient taking any medication? <input type="checkbox"/> No <input type="checkbox"/> Yes →If yes, please record below. <i>(If you answered "yes" to this question, please complete entire table below)</i>							
Agent Category	Agent Name	Indication	Taking at time of randomization?		Continuing? (after randomization)		
			No	Yes	No	Yes	Unknown
	Aspirin	(chronic low dose, prophylactic)					
Bisphosphonate							
Calcium							
Lipid Lowering Drug							
Cardiovascular Medication							
Other:							

6. OTHER MAJOR MEDICAL PROBLEMS (ongoing at baseline)
Have there been any major ongoing medical problems? <input type="checkbox"/> No <input type="checkbox"/> Yes → If yes, please enter details below:
Condition: (e.g. hypertension, diabetes, previous cancers, osteopenia)

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CDME

Physical Abnormalities

Check whether any abnormalities were found in the examination areas listed below. If "Yes", specify the abnormality. If area examined, check ND (Not Done).

Area of Examination:	Confirmation of Abnormality:	If yes, specify abnormality below:
Eyes:	(EYES) <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> ND	(EYESSP) _____
Head & Neck:	(HEAD) <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> ND	(HEADSP) _____
Respiratory:	(RESPTORY) <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> ND	(RESPSP) _____
Cardiovascular:	(CARDIO) <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> ND	(CARDIOSP) _____
Extremities:	(EXTREM) <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> ND	(EXTREMSP) _____

Concomitant Medications (MED)

mg
 mL or cc
 Units
 International Units
 Capsules

1. Total Daily Dose: (DOSE) Amount (DOSECH) *Additional Options Listed Below Units

2. Schedule: (SCHEDULE) *Additional Options Listed Below Select one

QD
 BID
 TID
 QID
 > 4x/Day

3. Indication for use: (INDICATI)

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Medical History (MHX)

Date of Examination: (EXAMDATE) _____ (mm/dd/yyyy)

Does this participant have diabetes? (DIABETES) No Yes
 Age at diabetes diagnosis? (AGEDIAG) _____ (xx)
 Currently under diabetic treatment? (TREATMNT) No Yes
 Total years on insulin? (YRSINSUL) _____ (xx)
 Total years on oral diabetic medication? (ORALMEDS) _____ (xx)
 Total years treated by diet? (DIET) _____ (xx)

Has this participant had cancer? (CANCER) No Yes
 Type of cancer: (CANCERTP) _____
 Breast
 Colon / Rectum
 Lung
 Prostate
 Melanoma
 *Additional Options Listed Below _____

If 'Other' cancer type, specify: (CANCERSP) _____

Year first diagnosed with cancer: (CANCERYR) _____ (xxxx)

Cancer recurrence in past 5 years? (CANCERRC) No Yes

Does this participant have heart disease? (HEARTDIS) No Yes

Has this participant had a stroke? (STROKE) No Yes
 If 'Yes', stroke was due to: (BLDORCLT) _____
 Bleed
 Clot
 Unknown

Has this participant had a TIA? (TIA) No Yes

Is this participant taking blood-thinning medication? (COUMADIN) No Yes
 If 'Yes', specify medical reason: (COUMADSP) _____

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Demographics (DEM)

Namecode: (NAMECODE)

Date of birth: (BIRTHDT)

Gender: (GENDER)

Race: (RACE)

(mm/dd/yyyy)

Male Female

American Indian or Alaskan Native
Asian
Black or African American
Native Hawaiian or Other Pacific Islander
White
*Additional Options Listed Below

Specify other: (RACEOTHR)

Ethnicity: (ETHNIC)

Not Hispanic or Latino
Hispanic or Latino
Unknown

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PreSAP

Patient subgroups will be identified according to the presence or absence of selected medical history terms and related information in records of screening or baseline clinic visits as follows (the absence of medical history terms does not confirm the absence of the respective risk factors in particular patients):

- Hypertension, including verbatim terms that correspond to International Classification of Diseases (ICD-9) codes for essential hypertension (401.x), hypertensive heart disease (402.x), hypertensive renal disease (403.x), hypertensive heart and renal disease (404.x), and secondary hypertension (405.x).
- Atherosclerotic heart disease, including verbatim terms that correspond to ICD-9 codes for acute myocardial infarction (410.x), other acute and subacute forms of ischemic heart disease (411.x), old myocardial infarction (412.x), angina pectoris (413.x), other forms of chronic ischemic heart disease (414.x), atherosclerotic cardiovascular disease (429.2), operations of vessels of heart (Procedure Code 36.x, including percutaneous transluminal coronary angioplasty), and carotid endarterectomy (Procedure Code 36.12).
- Cerebrovascular disease, including verbatim terms that correspond to ICD-9 codes for carotid artery occlusion (433.x, cerebral thrombosis and cerebral artery occlusion (434.x), transient cerebral ischemia (435.9), cerebrovascular accident (436), cerebrovascular disease (437.x).
- Diabetes, including verbatim terms that correspond to ICD-9 codes for diabetes mellitus (250.x) and diabetic neuropathy (357.2).
- Hyperlipidemia, including verbatim terms that correspond to ICD-9 codes for disorders of lipid metabolism (272.x).
- Smoking, determined as indicated by check box in records of screening or baseline clinic visits (smoker = checked box for either "current smoker" or "former smoker," and nonsmoker = checked box for "never smoked"; other tobacco use not considered).

The checkboxes referred to in the above description are shown below.

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LEAD-IN - MEDICAL HISTORY (PART 1 OF 2)

Date of Birth:

Day	Month	Year
<input type="text"/>	<input type="text"/>	<input type="text"/>

 Gender: Male Female Page not done

Race / Ethnic Origin:

Caucasian Black Asian Native American Hispanic / Latin American Other specify: _____

MEDICAL HISTORY:

Does the subject have a significant history of, or currently have, an abnormality or disease of the following systems?

If none, check here:

If "YES," specify finding or diagnosis (if known).

	NO	YES	
Ears, Nose, Throat:	<input type="checkbox"/>	<input type="checkbox"/>	_____
Ophthalmological:	<input type="checkbox"/>	<input type="checkbox"/>	_____
Neurological:	<input type="checkbox"/>	<input type="checkbox"/>	_____
Cardiovascular:	<input type="checkbox"/>	<input type="checkbox"/>	_____
Respiratory:	<input type="checkbox"/>	<input type="checkbox"/>	_____
Gastrointestinal:	<input type="checkbox"/>	<input type="checkbox"/>	_____
Renal:	<input type="checkbox"/>	<input type="checkbox"/>	_____
Musculoskeletal:	<input type="checkbox"/>	<input type="checkbox"/>	_____
Dermatological:	<input type="checkbox"/>	<input type="checkbox"/>	_____
Urogenital:	<input type="checkbox"/>	<input type="checkbox"/>	_____
Endocrine:	<input type="checkbox"/>	<input type="checkbox"/>	_____
Hematological:	<input type="checkbox"/>	<input type="checkbox"/>	_____
Hepatic:	<input type="checkbox"/>	<input type="checkbox"/>	_____
Metabolic:	<input type="checkbox"/>	<input type="checkbox"/>	_____
Allergies and Drug Sensitivity:	<input type="checkbox"/>	<input type="checkbox"/>	_____
Cancer:	<input type="checkbox"/>	<input type="checkbox"/>	_____
Psychological:	<input type="checkbox"/>	<input type="checkbox"/>	_____

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TOBACCO USE:

Cigarette History (choose one):

- Never smoked
 Current smoker

Number of cigarettes per day:

Number of years smoked:

- Former smoker

Date Quit:

Other Tobacco Use History (choose one):

- Never used
 Current user

per day:

Pipe: Pouches:

Cigar: Each:

Chew: Pouches:

Snuff: Cans:

- Former user

Date Quit:

MEDICATION:

Does subject have previous history of chronic (per protocol definition) NSAID use within the last 12 months? NO YES

If "YES", indicate month and year started and stopped:

Does subject routinely take aspirin for cardioprotection as per protocol? NO YES

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The Selenium Study

Section A: Current and Past Medical History

Next, I'm going to ask you some questions about your current and past medical history.

- | | <u>Eligible</u> | <u>Ineligible</u> |
|---|--------------------------------|----------------------------------|
| A1. Have you had an adenomatous colorectal polyp removed in the past six months? | 1 <input type="checkbox"/> Yes | 2 <input type="checkbox"/> No |
| A2. Have you <u>ever</u> been diagnosed with colon cancer? | 1 <input type="checkbox"/> No | 2 <input type="checkbox"/> Yes |
| A3. Have you had invasive cancer within the past five years that required medical excision, radiation therapy, or chemotherapy? | 1 <input type="checkbox"/> No | 2 <input type="checkbox"/> Yes |
| A4. Have you <u>ever</u> been diagnosed with Familial Adenomatous Polyposis (FAP)? | 1 <input type="checkbox"/> No | 2 <input type="checkbox"/> Yes |
| A5. Have you <u>ever</u> been diagnosed with Hereditary Non-Polyposis Colon Cancer (HNPCC)? | 1 <input type="checkbox"/> No | 2 <input type="checkbox"/> Yes |
| A6. Do you have plans to receive radiation therapy or chemotherapy in the future? | 1 <input type="checkbox"/> No | 2 <input type="checkbox"/> Yes |
| A7. Have you <u>ever</u> been diagnosed with rheumatoid arthritis? | 1 <input type="checkbox"/> No | 2 <input type="checkbox"/> Yes |
| A8. Do you currently have cardiac disease that is unstable despite medication? | 1 <input type="checkbox"/> No | 2 <input type="checkbox"/> Yes |
| A9. Do you currently have hypertension that is uncontrolled despite medication? .. | 1 <input type="checkbox"/> No | 2 <input type="checkbox"/> Yes |
| A10. Do you currently have poorly controlled diabetes mellitus despite medication? | 1 <input type="checkbox"/> No | 2 <input type="checkbox"/> Yes |
| A11. Do you currently have an insufficient or impaired kidney function? | 1 <input type="checkbox"/> No | 2 <input type="checkbox"/> Yes |
| A12. Have you ever been diagnosed with ulcerative colitis or Crohn's disease? | 1 <input type="checkbox"/> No | 2 <input type="checkbox"/> Yes |
| A13. Have you had a 10% unplanned weight loss in the past six months? | 1 <input type="checkbox"/> No | 2 <input type="checkbox"/> Yes |
| A14. Are you fully active and able to perform activities without restriction? | 1 <input type="checkbox"/> 0,1 | 2 <input type="checkbox"/> Other |
| Questions A15-A17a are for Females Only: | | |
| A15. Are you currently pregnant or lactating? | 1 <input type="checkbox"/> No | 2 <input type="checkbox"/> Yes |
| A16. Do you plan to become pregnant in the next 3 to 5 years? | 1 <input type="checkbox"/> No | 2 <input type="checkbox"/> Yes |
| A17. Are you surgically sterile or at least one year postmenopausal? | 3 <input type="checkbox"/> No | 1 <input type="checkbox"/> Yes |
| A17a. If No: Are you using reliable birth control? | 1 <input type="checkbox"/> Yes | 2 <input type="checkbox"/> No |

Section B: Drug History

The next few questions are about the prescription and non-prescription drugs you have taken previously and are currently taking.

- | | | <u>Eligible</u> | <u>Ineligible</u> |
|--|--------------------------------|--------------------------------|--------------------------------|
| B1. Do you currently take aspirin on a daily basis? | 3 <input type="checkbox"/> Yes | 1 <input type="checkbox"/> No | |
| B2. Are you currently taking a vitamin or mineral supplement? | 3 <input type="checkbox"/> Yes | 1 <input type="checkbox"/> No | |
| B3. Are you currently taking a COX-2 inhibitor or other NSAID regularly? ...3 <input type="checkbox"/> Yes | | 1 <input type="checkbox"/> No | |
| B3a. If Yes: Would you be willing to abstain from chronic use for the duration of the study with physician approval? | | 1 <input type="checkbox"/> Yes | 2 <input type="checkbox"/> No |
| B4. Are you currently taking any drugs to regulate your immune system? | | 1 <input type="checkbox"/> No | 2 <input type="checkbox"/> Yes |

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CELECOXIB/SELENIUM PHASE III STUDY
 Eligibility Form Part II: Aspirin, Other NSAID, and Selenium Assessment

Participant Label

Clinical Center: Visit:

Section E: Aspirin, Other NSAID Use:

E1. Is the participant currently taking aspirin or other NSAID? Yes No (Go to F1)

E2. List each aspirin or other NSAID.	E3. How much (DRUG NAME) is the participant currently taking?	E4. Reason (Mark all that apply)	E5. Doctor Prescribed	E6. Dose/Day
a. _____ DRUG NAME	_____ # UNITS DOSE (e.g. 2 pills) (e.g. 81 mg) <input type="checkbox"/> Day <input type="checkbox"/> QOD <input type="checkbox"/> Week <input type="checkbox"/> Month	<input type="checkbox"/> Arthritis <input type="checkbox"/> Cardiovascular <input type="checkbox"/> Pain <input type="checkbox"/> Other _____	<input type="checkbox"/> Yes <input type="checkbox"/> No	
b. _____ DRUG NAME	_____ # UNITS DOSE (e.g. 2 pills) (e.g. 81 mg) <input type="checkbox"/> Day <input type="checkbox"/> QOD <input type="checkbox"/> Week <input type="checkbox"/> Month	<input type="checkbox"/> Arthritis <input type="checkbox"/> Cardiovascular <input type="checkbox"/> Pain <input type="checkbox"/> Other _____	<input type="checkbox"/> Yes <input type="checkbox"/> No	
c. _____ DRUG NAME	_____ # UNITS DOSE (e.g. 2 pills) (e.g. 81 mg) <input type="checkbox"/> Day <input type="checkbox"/> QOD <input type="checkbox"/> Week <input type="checkbox"/> Month	<input type="checkbox"/> Arthritis <input type="checkbox"/> Cardiovascular <input type="checkbox"/> Pain <input type="checkbox"/> Other _____	<input type="checkbox"/> Yes <input type="checkbox"/> No	

E7. Total Routine Intake of Aspirin: _____ mg/day E8. Total Routine Intake of Other NSAID: _____ mg/day

- If the participant is routinely taking ≤ 81 mg/day of aspirin only, go to F1.
- If the participant is routinely taking >81 mg/day of aspirin only, complete E9.
- If the participant is routinely taking >81 mg/day of aspirin and other NSAID, complete E9 and E10.
- If the participant is routinely taking ≤ 81 mg/day of aspirin and other NSAID, complete E10.
- If the participant is routinely taking other NSAID only, complete E10.

E9. Is the participant willing to reduce their routine intake of aspirin to 81mg/day or less while on study (with physician approval)? Yes, Eligible No, Ineligible

E10. Is the participant willing to discontinue their other NSAID use while on study (with physician approval)? Yes, Eligible No, Ineligible

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Answer the following questions by placing an X in the appropriate box or writing the information requested. Mark only one answer per question unless otherwise stated. Please use a BLUE ballpoint pen to complete this form.

1. Do you consider yourself to be Hispanic or Latino?

- 1 Yes
- 2 No (Go to Question 2)
- 3 Don't know (Go to Question 2)

1A. Which Hispanic or Latino origin?

- 1 Mexican
- 2 Puerto Rican
- 3 Cuban
- 4 South or Central American
- 5 Don't know
- 6 Other, specify _____

2. What race do you consider yourself to be? You may select more than one.

- 1 White/Caucasian
Origins in any of the original peoples of Europe, the Middle East, or North Africa
- 2 Black/African-American
Origins in any of the black racial groups of Africa
- 3 Asian
Origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent, including Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam
- 4 American Indian or Alaska Native
Origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliation or community attachment
- 5 Native Hawaiian or other Pacific Islander
Origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands
- 6 Don't know
- 7 Other, specify _____

3. If you selected more than one racial group in question 2, which group do you identify with primarily?

- 1 White/Caucasian
- 2 Black/African-American
- 3 Asian
- 4 American Indian or Alaska Native
- 5 Native Hawaiian or other Pacific Islander
- 6 Unable to identify with only one group

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CELECOXIB/SELENIUM PHASE III STUDY
 Medical History Baseline Form

Participant Label

Clinical Center: [][] Visit: [][]

1. How would you rate your overall health at the present time? (Mark only one)

1 Excellent 2 Very Good 3 Good 4 Fair 5 Poor

2. Has a physician EVER diagnosed you with any of the following conditions? If yes, provide the first year you were diagnosed with this condition.

Condition	Yes (1)	No (2)	Year 1 st Diagnosed	Condition Not Previously Identified
1. Coronary heart disease				
a. Heart attack	<input type="checkbox"/>	<input type="checkbox"/>	[][][][]	_____
b. Angina	<input type="checkbox"/>	<input type="checkbox"/>	[][][][]	_____
c. Mitral or aortic valve disease	<input type="checkbox"/>	<input type="checkbox"/>	[][][][]	_____
d. Irregular heartbeat/dysrhythmias	<input type="checkbox"/>	<input type="checkbox"/>	[][][][]	_____
e. Congestive heart failure	<input type="checkbox"/>	<input type="checkbox"/>	[][][][]	_____
f. Cardiomegaly (enlarged heart)	<input type="checkbox"/>	<input type="checkbox"/>	[][][][]	_____
g. Abdominal aortic aneurysm	<input type="checkbox"/>	<input type="checkbox"/>	[][][][]	_____
h. Arteriosclerosis/atherosclerosis	<input type="checkbox"/>	<input type="checkbox"/>	[][][][]	_____
2. Hypertension (high blood pressure)	<input type="checkbox"/>	<input type="checkbox"/>	[][][][]	_____
3. Peptic ulcer	<input type="checkbox"/>	<input type="checkbox"/>	[][][][]	_____
4. Diverticulitis or diverticulosis	<input type="checkbox"/>	<input type="checkbox"/>	[][][][]	_____
5. Hemorrhoids	<input type="checkbox"/>	<input type="checkbox"/>	[][][][]	_____
6. Gallstones	<input type="checkbox"/>	<input type="checkbox"/>	[][][][]	_____
7. Chronic pancreatitis	<input type="checkbox"/>	<input type="checkbox"/>	[][][][]	_____
8. Hepatitis	<input type="checkbox"/>	<input type="checkbox"/>	[][][][]	_____
9. Cholecystectomy	<input type="checkbox"/>	<input type="checkbox"/>	[][][][]	_____
10. Small bowel removal/resection	<input type="checkbox"/>	<input type="checkbox"/>	[][][][]	_____
11. Large bowel removal/resection	<input type="checkbox"/>	<input type="checkbox"/>	[][][][]	_____
12. Chronic bronchitis	<input type="checkbox"/>	<input type="checkbox"/>	[][][][]	_____
13. Emphysema	<input type="checkbox"/>	<input type="checkbox"/>	[][][][]	_____
14. Stroke	<input type="checkbox"/>	<input type="checkbox"/>	[][][][]	_____
15. Arthritis	<input type="checkbox"/>	<input type="checkbox"/>	[][][][]	_____
16. Diabetes	<input type="checkbox"/>	<input type="checkbox"/>	[][][][]	_____
17. Any disease of the thyroid gland	<input type="checkbox"/>	<input type="checkbox"/>	[][][][]	_____
18. Kidney disease	<input type="checkbox"/>	<input type="checkbox"/>	[][][][]	_____
19. Ulcerative Colitis	<input type="checkbox"/>	<input type="checkbox"/>	[][][][]	_____
20. Crohn's Disease	<input type="checkbox"/>	<input type="checkbox"/>	[][][][]	_____

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CELECOXIB/SELENIUM PHASE III STUDY
 Concomitant Medications Form
 Page 1 of ____

SD

Participant Label

Clinical Center: |_|_| Visit Initiated: |_|_| Date Initiated: |_|_|-|_|_|-|_|_|
MO DD YR

Known Allergies: _____

Medication Name	Dose	Units	Frequency	Route	Indication	Start Date	Date/ Initials	Stop Date	Date/ Initials
						_ _ - _ _ - _ _ <small>MO DD YR</small>		_ _ - _ _ - _ _ <small>MO DD YR</small>	
						_ _ - _ _ - _ _ <small>MO DD YR</small>		_ _ - _ _ - _ _ <small>MO DD YR</small>	

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9. References

- ¹ Solomon SD, McMurray JJV, Pfeffer MA, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. *New Engl J of Med* 2005; 352: 1071-1080.
- ² Efron, B. The efficacy of Cox's likelihood function for censored data. *J Amer Stat Assn* 1977; 76:312--319.
- ³ Bailey K. Inter-study differences: how should they influence the interpretation and analysis of results. *Stat in Med* 1987; 6: 351-358/
- ⁴ Follman D, Proschan M. Valid inference in random effects meta-analysis. *Biometrics* 1999; 55: 732-737.
- ⁵ Pater J, Zee B, Myles J, Pignon J, Milan C, Sahnoud T, Torri V, Marsoni S. A proposal for a new approach to intergroup cancer trials. *Eur J Can* 1995; 31A: 1921-1923
- ⁶ Jennison C, Turnbull BW. *Croup Sequential Methods with Applications to Clinical Trials*. Boca Raton, FL. Chapman and Hall/CRC 2000.
- ⁷ Proschan M, Lan KKG, Wittes J. *Statistical Monitoring of Clinical Trials: A Unified Approach*. Springer 2006 (to appear).
- ⁸ Hedges LV, Olkin I. *Statistical Methods for Meta-analysis*. Orlando, FL: Academic Press 1985.
- ⁹ Smith TC, Spiegelhalter DJ, Thorns. A. Bavesian approaches to random-effects meta-analysis: comparative study. *Statistics in Medicine* 1995;14: 2685-2699.
- ¹⁰ Kaizar EE, Greenhouse JB, Selman H, Kelleher K. Do antidepressants cause suicidality in children: Bayesian meta-analysis (unpublished manuscript).
- ¹¹ Arber N, Solomon S, Wittes J. Cardiovascular outcomes for a long-term randomized colorectal adenoma chemoprevention trial of a once-daily dose of celecoxib (unpublished manuscript)

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¹³ Bresalier RS, Sandler RS, Quan H, et al.; Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial Investigators. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. *N Engl J Med* 2005;352:1092-102.

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Appendix 7: DSMB Plans for Studies Under CTSA Analysis

Proposed Charter For the Data and Safety Monitoring Board of the APC Trial (NCI Contract #N01-CN-95015, *Prevention of Sporadic Colorectal Adenomas with Celecoxib*)

I. Purpose

- To examine the endpoint and toxicity data from the APC Trial (NCI Contract #NO1-CN-95015, Pharmacia Protocol #IQ4-99-02-005) on a schedule specified by the protocol, and to make recommendations to the PI, NCI, and Pharmacia concerning the continuation, termination, or need for other modifications to the trial based on the observed beneficial or adverse effects of any of the treatments under study.
- To review the general progress of the study and to assist the PI, NCI, and Pharmacia in resolving any problems that might arise which would compromise the quality of the trial.

II. Membership

The membership of the Board reflects the disciplines and medical specialties necessary to interpret the data from the trial including experts in the fields of clinical prevention science, clinical trials, and biostatistics, in addition to clinicians knowledgeable about colon cancer prevention. Ad hoc member(s) may be appointed for a specific purpose, as circumstances require. The APC Trial Steering Committee will make such appointments. DSMB members are to remain completely independent – scientifically and financially - from the APC Trial.

The members of the DSMB are:

Gilbert Omenn, MD, PhD – University of Michigan, Ann Arbor

Steven Rosen, MD – Northwestern University & Lurie Comprehensive Cancer Center, Chicago

Robin Phillips, MD – St. Mark's Hospital, London, U.K.

Philip Taylor, MD, ScD – National Cancer Institute, Bethesda

Robert Makuch, MD – Yale University, New Haven

III. Responsibilities

Board members are expected to:

- Acquire a detailed knowledge of the goals, design, and plans for data and safety monitoring of the APC Trial
- Attend semi-annual meetings of the DSMB. Additional conference calls or meetings may be scheduled if necessary to address specific study issues or handle the workload in a reasonable manner.
- Review trial performance and interim analyses of outcome/cumulative toxicity data summaries to suggest additional analyses, or to determine whether the trial should continue as originally designed, should be changed, or should be terminated based on these data.
- Review major proposed modifications to the study prior to their implementation (e.g., termination, dropping a study arm based on toxicity results or other reported trial outcomes, modifying the target sample size)
- Review reports of related studies to determine whether the APC Trial should be changed or terminated.

- Provide study leadership with written information concerning findings for the trials as a whole, related to observed cumulative toxicities and any relevant recommendations related to continuing, changing, or terminating the trial.
- Determine whether and to whom outcome results should be released prior to reporting the study results.

IV. Meetings

The Board will meet to establish baseline procedures, and then meet semi-annually (every six months) during the course of the trial, and when a third of the cohort has completed their month 12 evaluations. Additional meetings may be scheduled as necessary for adequate monitoring.

Meetings of the DSMB will be closed to the public and all presented materials will be considered confidential. The agenda for the meeting will be developed by the PI in consultation with the study sponsors (NCI and Pharmacia). The business of the Board will be conducted in three parts:

- Part One may be attended by any member of the APC Trial study team including the PI; NCI Project Officer; NCI Contract Officer; Pharmacia medical monitor; statistical, monitoring, and/or auditing consultants. During this session, the PI (or designated other study representatives) will review the general conduct and progress of the trial with regard to accrual, comparability of the groups on baseline factors, quality control, protocol compliance, general toxicity issues, etc. All data will be presented by coded treatment arm, and outcome results will not be discussed during this session.
- Part Two will be a closed session involving the DSMB members and the coordinating center/statistical office statisticians. The statisticians will present and discuss the outcome results with the DSMB. Data will be presented by coded treatment arm, with the codes accessible only to the Board, and only upon request.
- Part Three will be a final executive session involving only DSMB members and will be held to allow the DSMB opportunity to discuss the general conduct of the trial and all outcome results, including toxicities and adverse events, develop recommendations, and take votes as necessary.

V. Interim Analysis

Interim reports will be prepared by the independent statistical consultant and distributed to the Board at least 7 days prior to a scheduled meeting. The contents of the report will be determined by the Steering Committee (PI, NCI, and Pharmacia) in consultation with the independent statistical consultant. Additions, supplements, and other modifications of these reports may be directed by the DSMB.

Interim reports will consist of two parts. Part I will provide information on accrual, baseline characteristics, data quality, safety, and other general information on study status. Part 2 will contain data on outcomes. Both parts of the report will be considered confidential, and all distributed copies will be collected by a person designated by the DSMB following the meeting.

Data files used for interim analysis will have undergone established editing procedures. The scheduled interim analysis for the primary efficacy comparison will be performed only when the data for the year one colonoscopy is available for all patients in the study.

VI. Recommendations from the DSMB

DSMB recommendations should be based on results for the trials being monitored as well as on data available to the DSMB from other studies. It is the responsibility of the coordinating center/statistical office, trial investigator(s), NCI program staff and statisticians, and individual DSMB members to ensure that the DSMB is kept apprised of non-confidential results from other related studies that become available, and of any programmatic concerns related to trials being monitored. It is the responsibility of the DSMB to determine the extent to which this information is relevant to its decisions related to specific trials.

Immediately following each meeting (within at least a week, in most instances), a written report summarizing the current status of the trial and the Board's recommendations will be prepared by the DSMB Chair (or his designee), circulated to the Board members for concurrence, and then given to the Steering Committee (PI, NCI, and Pharmacia). If the DSMB recommends a study change for patient safety or efficacy reasons, or that the study should be modified due to slow accrual, the Steering Committee must act to review the recommendation with the DSMB as expeditiously as possible. In the unlikely situation that the Steering Committee does not concur with the DSMB, then the NCI Division Director must be informed of the reason for disagreement. The trial Steering Committee, DSMB Chair, and the NCI Division Director or designee will be responsible for reaching a mutually acceptable decision about the study. Confidentiality must be maintained during these discussions. However, in some cases, relevant data may be shared with other selected trial investigators and NCI/Pharmacia staff to seek advice to assist in reaching a mutually acceptable decision. If a recommendation is made to change a trial for other than patient safety or efficacy reasons or for slow accrual, the DSMB will provide an adequate rationale for its decision. In the absence of disagreement, policies of the NCI must be followed in regard to amending the protocol or changing the award.

VII. Release of Outcome Data

In general, outcome data should not be made available to individuals outside of the DSMB until accrual has been completed and all patients have completed their treatment. At this time, the DSMB may approve the release of outcome data on a confidential basis to the trial Steering Committee for planning the preparation of manuscripts and/or to a small number of other investigators for purposes of planning future trials. Any release of outcome data prior to the DSMB's recommendation for general dissemination of results must be reviewed and approved by the DSMB.

VIII. Confidentiality Procedures for the DSMB Members

No communication, either written or oral, of the deliberations or recommendations of the DSMB will be made outside the DSMB except as provided for in this policy. Outcome results are strictly confidential and must not be divulged to any non-member of the DSMB, except as indicated above in the Recommendations section, until the recommendation to release the results are accepted and implemented. Each member of the DSMB, including non-voting members, must sign a statement of confidentiality.

IX. Conflict of Interest

The DSMB members must disclose any potential conflicts of interest, whether real or perceived. Conflict of interest can include personal, professional, financial or proprietary interests. Potential conflicts that develop during the member's tenure on the DSMB must also be disclosed. Disclosure is a key factor in protecting one's reputation and career from potential embarrassing or harmful allegations of inappropriate behavior. Such disclosure will also serve to protect the integrity of the DSMB and its role in monitoring and oversight of the study. Conflict of Interest Disclosure Forms must be signed prior to the first meeting of the DSMB. Failure to disclose a conflict of interest for the administrative review and response will lead to removal from the DSMB.

Important for understanding Conflict of Interest:

1. "Financial interest" means anything of monetary value, including but not limited to, salary or payment for services (e.g., consulting fees or honoraria) and equity interests (e.g., stocks, stock option other ownership interests), from a private held company, including equity in any pharmaceutical or biotechnology companies. Any financial interests of \$10,000 or above per company or entity need to be disclosed. This includes the financial interest of the DSMB participant's spouse and dependent children.
2. Intellectual property includes, but not limited to copyrights, patents, trademarks, trade names and trade secrets.
3. Conflict of interests may not necessarily involve financial gain, but rather could be related to personal aggrandizement based on insider knowledge.

Any possible conflict of interest relating to personal advancement should be disclosed and managed so as to avoid interference between the personal interest and the objective of this study to promote ethically and scientifically sound research.

The policies outlined above are intended to fulfill the "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" approved by the NCI Executive Committee on June 22, 1999.

Prevention of Sporadic Colorectal Adenomatous Polyps with Celecoxib - PRESAP
Data Safety Monitoring Board Charter

PROPOSED CHARTER

I. Purpose

- To examine the safety, toxicity, and endpoint data from the PreSAP Trial (Pharmacia Protocol EQ4-00-02-018) on a schedule specified by the protocol, and to make recommendations to Pharmacia concerning the continuation, termination, or need for other modifications to the trial based on the observed beneficial or adverse effects of any of the treatments under study.
- To review the general progress of the study and to assist Pharmacia in resolving any problems that might arise which would compromise the quality of the trial.

II. Membership

The membership of the DSMB reflects the disciplines and medical specialties necessary to interpret the data from the trial including experts in the fields of clinical prevention science, clinical trials, and biostatistics, in addition to clinicians knowledgeable about colon cancer prevention. Ad hoc member(s) may be appointed for a specific purpose, as circumstances require. The PreSAP Trial Steering Committee will make such appointments. DSMB members are to remain completely independent – scientifically and financially - from the PreSAP Trial.

The members of the DSMB are:

Contact information listed for all members in Appendix I.

Jeffrey A. Brinker, M.D.

Professor Jean Faivre

J. Jack Lee, Ph.D.

Alfred I. Neugut, M.D., Ph.D.

Sidney J. Winawer, M.D.

Member of DSMBs for all other active celecoxib protocols are listed in Appendix III.

III. Responsibilities

DSMB members are expected to:

- Acquire a detailed knowledge of the goals, design, and plans for data and safety monitoring of the PreSAP Trial as provided in the Study Protocol and Investigational Brochure
- Attend annual meetings of the DSMB. Additional conference calls or meetings may be scheduled if necessary to address specific study issues or handle the workload in a reasonable manner.
- Review trial performance and interim analyses of outcome/cumulative toxicity data summaries to suggest additional analyses, or to determine whether the trial should continue as originally designed, should be changed, or should be terminated based on these data.

Prevention of Sporadic Colorectal Adenomatous Polyps with Celecoxib - PRESAP
Data Safety Monitoring Board Charter

- Review major proposed modifications to the study prior to their implementation (e.g., termination, dropping a study arm based on toxicity results or other reported trial outcomes, modifying the target sample size)
- Review reports of related studies to determine whether the PreSAP Trial should be changed or terminated.
- Provide the study Steering Committee with written information concerning findings for the trials as a whole, related to observed cumulative toxicities and any relevant recommendations related to continuing, changing, or terminating the trial.
- Determine whether and to whom outcome results should be released prior to reporting the study results.
- Maintain written records of all meeting minutes, assessments and recommendations, material reviewed, and communications between the DSMB and Pharmacia contacts.

IV. Role of the Steering Committee

The Core Steering Committee consists of

Co-Principal Investigators

Bernard Levin, MD
Nadir Arber, MD

Pharmacia Oncology Clinical Vice President

Ivan Horak, MD

Pharmacia Medical Directors

Francisco Sapunar, MD
Aby Buchbinder, MD

The Core Steering committee meets on a weekly/monthly basis.

Pharmacia Study Contact information, including Study Management and Outside Consultants, is listed in Appendix II.

The Greater Steering Committee also consists of

Outside Consultants

Anne Zauber, PhD
Andrew Dannenburg, MD
 Wendy Atkins, PhD
 Reinhold Stockbrugger, MD
 Raymond Dubois, MD, PhD
 Benjamin Wong, MD

Steering Committee responsibilities include the oversight of the operational conduct of the study, and authorization, review and approval of protocol modifications based on operational concerns or emerging information relevant to either the study agent or the study population or endpoints. The Steering Committee will approve the members of the statistics committee responsible for all study analyses, and appoint the members of the DSMB. The greater Steering Committee will meet on a semi-annual basis and will have additional meetings and communications as required.

Prevention of Sporadic Colorectal Adenomatous Polyps with Celecoxib - PRESAP
Data Safety Monitoring Board Charter

IV. Meetings

The DSMB will meet to establish baseline procedures, and then meet annually (every twelve months) during the course of the trial, and when a third of the cohort has completed their month 12 evaluations. Additional meetings may be scheduled as necessary for adequate monitoring.

Meetings of the DSMB will be closed to the public and all presented materials will be considered confidential. The agenda for the meeting will be developed by the Core Steering Committee. During each formal meeting, the business of the Board will be conducted in three parts:

- Part One may be attended by any member of the Core Steering Committee and/or designated delegates including statistical, monitoring, and/or auditing consultants. During this session, the designated study representative will review the general conduct and progress of the trial with regard to accrual, comparability of the groups on baseline factors, quality control, protocol compliance, etc. All data will be presented by coded treatment arm, and outcome results will not be discussed during this session.
- Part Two will be a closed session involving the DSMB members and the coordinating center/statistical office statisticians. The statisticians will present and discuss the outcome results with the DSMB. Data will be presented by coded treatment arm, with the codes accessible only to the Board, and only upon request.
- Part Three will be a final executive session involving only DSMB members and will be held to allow the DSMB opportunity to discuss the general conduct of the trial and all outcome results, including toxicities and adverse events, develop recommendations, and take votes as necessary.

Pharmacia will notify the DSMB of any new safety information prior to scheduled meetings.

V. Recordkeeping

The DSMB Chair will maintain written records of all meeting minutes, assessments and recommendations, material reviewed, and communications between the DSMB and Pharmacia contacts. Meeting minutes must be complete within 5 working days of the last day of each DSMB meeting.

Records must be available for inspection upon request from regulatory/health authorities.

All written records and the material reviewed will be archived by Pharmacia upon the dissolution of the DSMB.

Prevention of Sporadic Colorectal Adenomatous Polyps with Celecoxib - PRESAP
Data Safety Monitoring Board Charter

VI. Interim Analysis

Interim reports will be prepared by the statistical consultant and distributed to the DSMB at least 7 days prior to a scheduled meeting. The contents of the report will be determined by the Greater Steering Committee in consultation with the independent statistical consultant. Additions, supplements, and other modifications of these reports may be directed by the DSMB.

Interim reports will consist of two parts. Part I will provide information on accrual, baseline characteristics, data quality, safety, and other general information on study status. Part 2 will contain data on outcomes. Both parts of the report will be considered confidential.

Data files used for interim analysis will have undergone established editing procedures. The scheduled interim analysis for the primary efficacy comparison will be performed only when the data for the year one colonoscopy is available for all patients in the study.

Data reports provided to the DSMB for Interim Analysis will be provided in a blinded format with treatment groups labeled as A & B in order to assess a greater effect or safety profile in one group as compared to the other.

VII. Recommendations from the DSMB

DSMB recommendations should be based on results for the trials being monitored as well as on data available to the DSMB from other studies. It is the responsibility of the trial investigator(s), Pharmacia study staff and statisticians, and individual DSMB members to ensure that the DSMB is kept apprised of non-confidential results from other related studies that become available, and of any programmatic concerns related to trials being monitored. It is the responsibility of the DSMB to determine the extent to which this information is relevant to its decisions related to specific trials.

Immediately following each meeting (5 working day maximum), a written report summarizing the current status of the trial and the Board's recommendations will be prepared by the DSMB Chair (or his designee), circulated to the Board members for concurrence, and then given to the Steering Committee. If the DSMB recommends a study change for patient safety or efficacy reasons, or that the study should be modified due to slow accrual, the Steering Committee must act to review the recommendation with the DSMB as expeditiously as possible. In the unlikely situation that the Steering Committee does not concur with the DSMB, then the reason for disagreement will be documented in the study file. The study Steering Committee and the DSMB Chair will be responsible for reaching a mutually acceptable decision about the study. Confidentiality must be maintained during these discussions. However, in some cases, relevant data may be shared with other selected trial investigators and Pharmacia staff to seek advice to assist in reaching a mutually acceptable decision if agreed upon by both parties. If a recommendation is made to change a trial for other than patient safety or efficacy reasons or for slow accrual, the DSMB will provide an adequate rationale for its decision. In the absence of disagreement, policies of Pharmacia must be followed in regard to amending the protocol or changing the award.

Prevention of Sporadic Colorectal Adenomatous Polyps with Celecoxib - PRESAP
Data Safety Monitoring Board Charter

VIII. Release of Outcome Data

In general, outcome data should not be made available to individuals outside of the DSMB until accrual has been completed and all patients have completed their treatment. At this time, the DSMB may approve the release of outcome data on a confidential basis to the trial Steering Committee for planning the preparation of manuscripts and/or to a small number of other investigators for purposes of planning future trials. Any release of outcome data prior to the DSMB's recommendation for general dissemination of results must be reviewed and approved by the DSMB.

IX. Confidentiality Procedures for the DSMB Members

No communication, either written or oral, of the deliberations or recommendations of the DSMB will be made outside the DSMB except as provided for in this policy. Outcome results are strictly confidential and must not be divulged to any non-member of the DSMB, except as indicated above in the Recommendations section, until the recommendation to release the results are accepted and implemented. Each member of the DSMB, including non-voting members, must sign a statement of confidentiality.

X. Conflict of Interest

The DSMB members must disclose any potential conflicts of interest, whether real or perceived. Conflict of interest can include personal, professional, financial or proprietary interests. Potential conflicts that develop during the member's tenure on the DSMB must also be disclosed. Disclosure is a key factor in protecting one's reputation and career from potential embarrassing or harmful allegations of inappropriate behavior. Such disclosure will also serve to protect the integrity of the DSMB and its role in monitoring and oversight of the study. Conflict of Interest Disclosure Forms must be signed prior to the first meeting of the DSMB. Failure to disclose a conflict of interest for the administrative review and response will lead to removal from the DSMB.

Important for understanding Conflict of Interest:

4. "Financial interest" means anything of monetary value, including but not limited to, salary or payment for services (e.g., consulting fees or honoraria) and equity interests (e.g., stocks, stock option other ownership interests), from a private held company, including equity in any pharmaceutical or biotechnology companies. Any financial interests of \$10,000 or above per company or entity need to be disclosed. This includes the financial interest of the DSMB participant's spouse and dependent children.
5. Intellectual property includes, but not limited to copyrights, patents, trademarks, trade names and trade secrets.
6. Conflict of interests may not necessarily involve financial gain, but rather could be related to personal aggrandizement based on insider knowledge.

Any possible conflict of interest relating to personal advancement should be disclosed and managed so as to avoid interference between the personal interest and the objective of this study to promote ethically and scientifically sound research.

Prevention of Sporadic Colorectal Adenomatous Polyps with Celecoxib - PRESAP
Data Safety Monitoring Board Charter

APPENDIX I**STUDY DSMB CONTACT INFORMATION****Sidney J. Winawer, M.D.**

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APPENDIX II

PHARMACIA STUDY CONTACTS

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APPENDIX II
PHARMACIA OUTSIDE CONSULTANTS (cont.)

PreSAP Steering Committee Members

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St. Mark's Hospital
Northwick Park, Watford Road
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APPENDIX III
CELECOXIB: ACTIVE SAFETY MONITORING BOARDS

IQ4-99-02-005

Prevention of Sporadic Adenomas with Celecoxib
(NCI Sponsored)

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ADAPT Treatment Effects Monitoring Committee Policy (as of 20. Nov 02)

The purpose of this document is to outline the policies related to treatment effects monitoring, including the charge, composition, and operating procedures of the Treatment Effects Monitoring Committee (TEMC). The policies below were discussed and amended at several Steering Committee meetings and conform to the guidelines of the National Institute on Aging.

Charge

- The charge of the Treatment Effects Monitoring Committee (TEMC) is to protect the interests of ADAPT participants via review of accumulating data on the safety and efficacy of the study drugs
- The TEMC reports to the ADAPT Steering Committee and the National Institute on Aging; the institutional review boards of the participating institutions will be sent summary reports of its recommendations
- The TEMC may recommend stopping the trial before its planned conclusion in the face of convincing evidence of a treatment difference in adverse events or in the incidence of Alzheimer's disease; however, it is not expected that the TEMC will stop the trial early because of attenuation of decline in cognitive measures alone (i.e., without simultaneous demonstration of efficacy in reducing incidence of Alzheimer's disease)

Composition of the TEMC

- The TEMC is comprised of individuals who are independent of ADAPT (voting members) and of designated representatives of ADAPT (non-voting) and that the listing of membership, as represented in study documents and publications, include both types of members
- Non-voting members are seated at par with voting members in all aspects relating to monitoring, except as regards the right to vote, that is, that all members are present for all presentations, discussions., deliberations, and votes relating to treatment effects monitoring (i.e., no executive sessions for results-based presentations, discussions, deliberations, or votes)
- Voting members:
 - Are independent, i.e., not involved in the conduct of ADAPT and expected to be free of affiliations with the manufacturers of naproxen or celecoxib
 - Represent several fields of expertise, including biostatistics, psychiatry, neurology, and bioethics
- Non-voting members:
 - Are representatives of the study leadership
 - Represent various aspects of the conduct of the trial, including protocol implementation, oversight of the protocol, and data analysis
- The membership of TEMC shall include at least two Study Officers

Appointment and meetings

- Voting members are appointed by the Study Chair with the advice and consent of the Steering Committee and the National Institute on Aging
- Term of appointment is for the duration of the trial
- The TEMC will meet at least twice per year (in person or by conference call); in addition, they may elect to have *ad hoc* meetings or teleconferences at their initiative
- Voting members are expected to attend all meetings of the TEMC; they may be dismissed by the Study Chair with the advice and consent of the Steering Committee if they miss more than two consecutive meetings

Excerpted from ADAPT L&M\PPM\PPM55.wpd

- Meetings of the TEMC may be called by any member (voting or non-voting) if seconded by at least one other member

Operating procedures

- Reports presented to the TEMC will, at a minimum, include treatment group comparisons of baseline characteristics, incidence of Alzheimer's disease, changes overtime in cognitive measures, mortality, and adverse events
 - The Coordinating Center will propose a report template for the TEMC's consideration at their first meeting after enrollment into the trial has begun
 - The Coordinating Center will notify the Chair of the TEMC if concerns related to safety are noted so that the TEMC can call an *ad hoc* meeting; in such a circumstance, the Coordinating Center will produce an "unscheduled" report of data analyses requested by the TEMC
- The TEMC members will not be masked to treatment assignments and treatments in monitoring reports will not be coded
- ADAPT data are confidential and must not be discussed outside the TEMC meetings
- Constraints on the monitoring of data, such as the use of stopping rules, limits on the number of interim looks, and restrictions on the data reviewed, must be presented to and reviewed and approved by the Steering Committee
- The Study Officers may monitor for safety independent of the TEMC
- The Study Officers are not fettered in regard to communications and access to study results deemed necessary for proper and safe conduct of the trial or necessary for addressing logistic issues in presenting recommendations to study investigators or in planning for implementations of such recommendations

Requirements for a quorum

- Attendance of either the Chair or Vice Chair of the TEMC and of the majority of the voting members
- Attendance of at least one Study Officer

Voting

- Voting will occur in the presence of the full committee (both voting and non-voting)
- Proxy or absentee votes are not permitted

Recommendations by the TEMC

- The summary recommendation to continue the trial will be forwarded by the Chair of the TEMC to the Chair of ADAPT and to the National Institute on Aging (NIA). The Coordinating Center will then submit the summary recommendation to all IRBs.
- In the event of a recommendation for stopping the trial, the Chair of ADAPT will forward the recommendation to the ADAPT Steering Committee for review. Only after review by the ADAPT Steering Committee, will the Coordinating Center submit the summary recommendations to all IRBs.
- The Steering Committee will review and vote on a recommendation to stop the trial
 - If approved, the Study Chair will communicate the decision to the sponsors, research group, and other appropriate entities, and the Steering Committee will proceed with plans to implement the decision

Excerpted from ADAPT L&M\PPM\PPM55.wpd

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- In the event that the Steering Committee disagrees with the recommendation of the TEMC:
 - o The Steering Committee will initiate a dialogue with the TEMC regarding the decision
 - o Rejection of the recommendations requires a vote to reject by 2/3 of the Steering Committee
 - o In this event, the Steering Committee shall write and publish a document providing the rationale for the action
 - A summary report of the TEMC's recommendation will be provided to the institutional review boards of the participating institutions; should the Steering Committee disagree with the recommendations, it also will send a summary report to the institutional review boards
 - The Coordinating Center notifies its IRB of meetings of the TEMC within 60 days of such meetings, and at the same time distributes such notices to center directors for distribution to their respective IRBs; such notices to include the date of the meeting, attendance, types of data reviewed including specific mention of safety data, and recommendations
-

Excerpted from ADAPT L&M\PPM\PPM55.wpd

**GUIDELINES FOR THE NATIONAL CANCER INSTITUTE OF
CANADA CLINICAL TRIALS GROUP (NCIC CTG) DATA SAFETY MONITORING
COMMITTEE
October 4, 2001**

NCIC procedures for monitoring Phase III trials are in accordance with the NCI Cooperative Group Data Monitoring Committee policy. A single Data Safety Monitoring Committee (DSMC) is responsible for all studies led by the NCIC CTG.

AUTHORITY:

The NCIC CTG DSMC is an advisory committee to the Group Chair.

MEETINGS:

The NCIC CTG DSMC will review all Phase III trials at 6 monthly intervals. At least one of these meetings will be face-to-face, generally at the NCIC CTG spring meeting, whereas if appropriate, the second may be in the form of a conference call.

A current data report for each trial is sent to the DSMC members by the NCIC CTG central office allowing sufficient time for the DSMC members for review prior to the meeting. Toxicity data for phase III trials will be presented in the reports by treatment arm whether a trial is blinded or unblinded. For blinded trials the treatment arms will not be identified unless requested by the DSMC in the case of safety concerns.

RESPONSIBILITIES:

The NCIC CTG DSMC will be responsible for:

1. Reviewing all toxicity data from ongoing trials. Where necessary, they will make recommendations for corrective action which may include early closure, suspension or modification of a trial, or changes in Consent Forms.
2. Review all planned interim analyses, recognizing the confidentiality of the data and making recommendation to the group Chair about continuing, modifying or stopping the study.
3. Assessing the accrual rates to all studies to ensure that their completion remains feasible. Where this is judged not to be the case, the Committee will recommend closure to the group Chair.
4. Reviewing external studies or other data which might impact upon ongoing trials of the NCIC CTG. If necessary the Committee will make recommendations for modifications or closure of studies based upon external data. It is the responsibility of the site group executives to review all external data relating to ongoing trials and to inform the chair of the DSMC of any data that could be relevant to NCIC CTG trials. This item should be placed on the agenda of each site group executive meeting.
5. Review of major modifications to the study proposed by the trial committee prior to implementation (eg. early termination, an increase in sample size).

-
6. Determining whether and to whom outcome results should be released prior to reporting of study results at the time specified in the protocol.

MEMBERSHIP

The NCIC CTG DSMC will consist of at least 9 members of whom at least 7 will be voting members. Voting members will include 1 oncologist from each of the 3 major disciplines, 1 statistician external to the NCIC, and 1 patient representative. An NCIC CTG Group Statistician and a representative of the US National Cancer Institute will normally attend the meetings. Membership will be restricted to 5 years, and 2 members will rotate off the Committee each year.

Appointment of new members, and of the DSMC chairperson will be the responsibility of the NCIC CTG Clinical Trials Committee.

Approved: October 9, 2001

**POLICIES AND PROCEDURES FOR THE NEI INTRAMURAL
CLINICAL TRIAL DATA AND SAFETY MONITORING COMMITTEE
(DSMC)**

1. PURPOSE

The functions of the NEI Data and Safety Monitoring Committee (DSMC) include:

- to review and approve NEI intramural intervention protocols prior to implementation and, as appropriate, recommend design changes
- to review and approve major changes to study protocols
- to examine endpoint and toxicity data from NEI intramural intervention protocols on a schedule to be determined based on the protocol
- to make recommendations to the NEI concerning continuation, termination, or other modification of studies based on the observed beneficial or adverse effects of any of the treatments under study
- to review the general progress of the study and to assist in resolving any problems which may arise
- to review abstracts and manuscripts.

2. MEMBERSHIP

The DSMC members and chairperson are appointed by the NEI Clinical Center Director and reflect the disciplines and medical specialties necessary to interpret the data from the studies performed at the NEI Clinical Center. The core DSMC will consist of an interdisciplinary group of four to six permanent members who will include at least one statistician and one ethicist. The other permanent members will be ophthalmologists acquainted with the research issues peculiar to the various trials. On occasion a trial will require expertise in other areas such as pediatrics, endocrinology, infectious diseases, etc., and the core committee will be supplemented by appropriate ad hoc members. To assure the independence and impartiality of the DSMC, members will have no professional or financial interests dependent on the outcome of the trials. Members will be appointed to serve terms of indefinite length by the NEI.

3. DSMC FUNCTIONS

The DSMC has the general charge of ensuring, through advice to the investigators and the NEI, that the trial is conducted safely and ethically and that the trial meets its primary objectives. This includes the interests of currently enrolled patients, but also includes the interests of patients to be enrolled in the future and patients outside the study. To these ends the committee has the following functions:

Protocol Review. The DSMC can effectively advise on conduct of the trial only if its members agree with the premise, purpose, design, and procedures of the trial. Therefore, the first function of the DSMC is to review and approve the protocol before initiation of the trial. In this process the DSMC will interactively engage study investigators in discussions of modifications and improvements.

Review of Safety Data. The Data Coordinating Center (DCC) provides the DSMC, on a regular schedule determined by the needs of the trial, reports of adverse events among trial participants. Deaths or other serious events are reported to the DSMC Chair and appointed Medical Monitors as soon as they occur. To assure patient safety in each trial, the committee will develop individualized methods for monitoring adverse events.

Review of Efficacy Data. On a schedule determined before data are collected, the DSMC may examine outcome data, provided by the DCC, for early evidence of efficacy or lack of it. Throughout the trial the committee will monitor study assumptions about incidence rates and sample size. The DSMC will evaluate, as appropriate, outcome data according to guidelines for data monitoring outlined in published procedures (e.g., Pocock [1], O'Brien and Fleming [2], and Lan and DeMets [3]). Based on data reviewed at these interim evaluations, the committee may recommend early termination of the trial either because of established efficacy of treatment or because of the unlikelihood that a meaningful assessment of treatment effect could be established by the planned end of the trial. The DSMC may also recommend extensions in trial length or increases in sample size, as well as other relevant modifications to the protocol.

Advice on Data Analysis. The DSMC will review plans for data analysis and advise the DCC on the content of its periodic reports and on the specific analyses to be performed.

Review of Data Quality and Trial Operations. To ensure the highest possible quality of the data, the committee will regularly monitor aspects of the functioning of the DCC, which include the following:

- the flow of study forms,
- the timeliness of safety and efficacy data,
- compliance to the study protocol, by patients and investigators,
- the number of study withdrawals,
- the number of study anomalies including codebreaking and non-compliance to randomized study assignment,
- the recruitment and eligibility rates,
- and any other measures reflecting quality of data.

On the basis of such a review the DSMC will recommend any necessary modifications in trial operations.

4. TYPE OF STUDIES REQUIRING A DSMC

A DSMC will be convened to make disinterested and unbiased evaluations of emerging data from NEI intramural intervention protocols.

5. MEETINGS

The Committee will meet at least three times a year. Additional meetings may be scheduled when necessary for adequate monitoring. Any member of the Committee may request a meeting if they feel data provided within interim reports warrant an additional meeting. The agenda for each meeting will be developed by the NEI and DCC in conjunction with the DSMC Chair. Material presented at all sessions is confidential.

At the initial DSMC review for a proposed clinical trial the committee will discuss the objectives of the protocol, suggest revisions, and issue formal approval, with conditions if appropriate. The committee may reject a proposal.

When data are to be reviewed, the meeting will be divided into an open session, a closed session and a closed administrative session. The open session may be attended by parties with interest in the trial. In the open session aggregate statistics (i.e., total, with no treatment group breakdown) on trial progress such as patient accrual, baseline characteristics, and forms statistics are presented and discussed. In the closed session data including outcome results by randomized treatment group are presented and discussed. For this reason only DSMC members and DCC representatives attend the closed session. Study investigators may be invited to the discussions at times during the closed session to provide information, but they may not view the documents under discussion or otherwise compromise the study masking. In the administrative session, attended only by voting DSMC members and an NEI representative, the committee discusses, votes, and makes its recommendations and decisions. If there is a tie, the Chair will be the deciding vote. If there is not unanimous support for a decision, the recommendations will include a minority report. These recommendations are then sent to the Director of the National Eye Institute.

6. REPORTS

After the DSMC's written report has been reviewed by the NEI Director, the report will be sent to the study investigators and the IRB of each participating institution.

7. INTERACTION WITH IRBs

As described above, the DSMC will review (by meeting or mail ballot) each proposed protocol and collaborate with investigators on a draft that meets DSMC approval. Investigators will then provide to the IRBs of all involved institutions the DSMC-approved protocol and a copy of the DSMC report(s) antecedent to it. The IRBs may use these reports to expedite their own review. In the event an IRB requires revision or other action on the protocol, a copy of the IRB report will be forwarded to the DSMC for its consideration and advice to the investigators. The IRB must review the final protocol prior to initiation of the study. The investigator shall mail the final IRB approved protocol to the DSMC.

For all ongoing trials the DSMC will have regular meetings to review study safety and efficacy data as described above. The committee may also require ad hoc meetings to address unexpected or exigent safety events. Each of these meetings will result in a formal recommendation to the Director of the NEI concerning the continuation of the study. When any of these meetings results in a change in study protocol, the relevant information will be sent promptly to the IRBs. To assist the IRBs in their annual review of ongoing study protocols, the DSMC will routinely provide the summary recommendations from each DSMC meeting to all appropriate IRBs. A DSMC member will be available to attend IRB meetings, if necessary, for discussion of any safety issues or any recommendation for a change in study protocol.

8. PUBLICATION POLICY

Abstracts or manuscripts reporting data results from intervention studies will be submitted by the Coordinating Center for DSMC review prior to any presentation or manuscript submission. For randomized studies, no outcome data should be presented until after a manuscript has been accepted for publication. Presentation of material previously approved for publication or presentation by the committee need not be submitted for a second review, unless requested by the Principal Investigator or the DSMC.

Review of Abstracts and Manuscripts

The DSMC will review the trial's major efficacy and safety manuscript prior to submission for publication consideration and will be asked to respond by individual ballot regarding approval or disapproval of the manuscript's conclusions. A summary of the DSMC's response regarding the manuscript's suitability for submission will be submitted as a recommendation to the NEI Director. The DSMC, through its regular quarterly meetings, will have an opportunity to review data summaries and analytic methodology intended for incorporation in the manuscript.

Secondary manuscripts, reporting on secondary outcome measures defined in the protocol or manuscripts reporting baseline data, do not require review and approval by the DSMC, but the DSMC members will receive copies of all such manuscripts for their interest. However, the DSMC will have the right to request a role in the formal review and approval process of a secondary manuscript that has important implications for the interpretation of the results from a study.

The DSMC must review abstracts reporting, prior to manuscript publication, (1) the primary study results or (2) primary outcome data from the study, even if not reporting by treatment group, prior to submission. The Coordinating Center will submit the abstracts to the DSMC for review at least 2 weeks in advance of the submission due date. If the DSMC recommends disapproval, this recommendation will be forwarded to the NEI Director with a final evaluation provided by the NEI Director. All other abstracts that do not contain treatment outcomes, will be submitted to the Clinical Director for review at least 2 weeks in advance of the submission due date. The Clinical Director will then decide whether the abstracts need to be reviewed by the DSMC.

Publicity for Study Results

As with the policy for manuscripts and abstracts, the DSMC must review public release of study findings. Any study results that fall under the policy requiring DSMC approval for a manuscript or abstract also applies to a press release or any other form.

References

- [1] Pocock, SJ (1977) Group sequential methods in the design and analysis of clinical trials.
Biometrika, 64:191-199.
- [2] O'Brien, PC and Fleming,TR (1979) A multiple testing procedure for clinical trials.
Biometrics, 35:549-556.
- [3] Lan, KKG and DeMets,DL (1983) Discrete sequential boundaries for clinical trials.
Biometrika, 70:659-663.

Colon Cancer Prevention Program Project (CA 41108)
Dr. Peter Lance, Principal Investigator

Data and Safety Monitoring Plan

The Colon Cancer Prevention Program Project (CCPPP) has a formal External Data and Safety Monitoring Committee (EDSMC) comprised of the following members:

Ross Prentice, M.D. (Statistician, Fred Hutchinson Cancer Center Research Center)
Edward Giovannucci, Ph.D. (Epidemiologist, Harvard University)
Jeffrey Borer, M.D. (Cardiologist, Cornell University)
David Ransohoff, M.D. (Clinical Trialist and Epidemiologist, University of North Carolina, Chapel Hill)
Linda Hicks (Patient representative)

CCPPP also has a formal Internal Data and Safety Monitoring Committee (IDSMC) with the following membership:

Joseph Alpert, M.D., Cardiologist
Ana Maria Lopez, M.D., Medical Oncologist
Tom Miller, M.D., Medical Oncologist
Richard Sampliner, M.D., Gastroenterologist
James Warneke, M.D., Surgical Oncologist

The IDSMC assists with monitoring of adverse events in preparation of reports for EDSMC meetings.

The EDSMC meets at least twice a year, usually once in person and once via teleconference. Interim meetings, if needed, are held via teleconference. During the open sessions at these meetings, only blinded data (combined over randomization groups) are presented; the Study Investigators and Internal Data and Safety Monitoring Committee members, who attend such sessions, include:

Dr. David Alberts, Principal Investigator
Dr. Peter Lance, Project Leader, Project I
Dr. Sylvan Green, Biostatistician, Biometry Core
Dr. Elena Martinez, Project Leader, Project III
Dr. Paul Hsu, Biostatistician
Fang Wang, Data Manager
Liane Fales, R.N., Clinical Coordinator, Project I
Stefanie Obara, B.S., C.R.A., Regulatory Affairs Officer, Project I
Dr. Joseph Alpert, Cardiologist, IDSMC
Dr. Richard Sampliner, IDSMC

Drs. Green and Hsu are present while unblinded data (by randomization groups) are presented and discussed by the EDSMC in closed session.

The EDSMC reviews data from the clinical trial for participant safety. In general, data are provided on participant accrual and randomization, baseline characteristics of participants (e.g., gender, age, race, baseline polyps), follow-up colon examinations, and off-treatment status.

Protocol deviations are presented to the EDSMC for review. Protocol modifications are also discussed.

During the open session, only blinded data (combined over randomization groups) are presented. In the closed session, attended by the members of the EDSMC and by the biostatisticians (and a Program Coordinator who keeps the minutes), data are presented according to randomized intervention group; thus the EDSMC can have access to unblinded data. Participant safety is assessed through a presentation of toxicity data for both treatment related and non-treatment related events, blood chemistries and serious adverse events as reported to the NCI, FDA, and the University of Arizona Human Subjects Committee (UA HSC). These events include all reports of death, grade 3 or higher “expected” toxicities, and any other grade 3 or higher events for which the Principal Investigator and members of the EDSMC believe there is a reasonable possibility that the event may have been caused by the study intervention. All other reported adverse events are presented for review by the EDSMC. The EDSMC reviews data for imbalances in intervention groups to assess for possible unknown risk. The EDSMC is typically also presented with outcome data and any interim analyses, if applicable.

At the end of the meetings, the EDSMC is given the opportunity to discuss the trial(s) and the data presented privately. The EDSMC then recommends to the Principal Investigator any additional data which they would like to have reported, any concerns regarding the safety and conduct of the trial(s), and any recommendations regarding the continued conduct of the trial(s). Actions taken due to recommendations made by the EDSMC are discussed at the subsequent meeting. The biostatisticians in the Biometry Core are responsible for preparation of materials for presentation at EDSMC meetings and act as liaison between the Principal Investigator and the EDSMC.

In the Selenium Study, most of the outcome information is based on the scheduled follow-up colonoscopy for each participant, so there is little information on outcomes during the early part of the trial. Furthermore, given the nature of this trial, as a study of prevention of adenomas, in a setting of appropriate surveillance for participants in all intervention groups, there is not thought to be a need for formal statistical testing for early stopping based on outcome data (recurrent adenomas). However, at the point in the trial when outcome data from follow-up colonoscopies become available, data will be reported yearly (in closed session) to the EDSMC on adenoma rates, separately by randomized intervention group. Analyses can be performed that account for varying periods of follow-up across participants. The EDSMC will review the accumulating outcome data (adenomas and/or colon cancers) and evaluate the results in the context of results of any other trials that might be reported in the interval. It is not anticipated that there would be reason to terminate this trial early, but the EDSMC can make such a recommendation if warranted.

A summary of the meeting and all recommendations from the EDSMC are provided to the NCI and the University of Arizona Human Subject’s Committee, and the Institutional Review Boards involved in the studies. Any recommended significant changes require approval from the UA HSC prior to implementation. Approved recommendations are reported to the NCI.

All Serious Adverse Events are reported following local IRB and federal regulations. SAEs are initially sent to the Clinical Coordinator and all SAEs are reviewed by the investigator. Upon review and signature by the PI, all SAEs are forwarded to the appropriate institutions including the local IRB, NCI, drug manufacturers, the FDA (when necessary) and collaborating sites for forwarding to their respective IRBs.

Any information gained which presents a situation where the trial(s), or part of the trial(s) may need to be suspended or terminated will be promptly forwarded to the NCI program director responsible for the grant and the UA HSC.

The quality assurance/quality control (QA/QC) program stems from the Biometry and Data Management Core. There is a smooth flow of data between clinical sites (including the collaborating sites) and the Core. Specific procedures and data collection forms are used to capture the data and to address quality assurance issues. Forms are reviewed for accuracy and completeness once they arrive at the Data Management office, and queries are sent back to the clinic as needed. Double entry of the data is performed as a quality assurance measure by data entry students. Once entered, data are cleaned by the Data Manager. Further queries are sent to the clinics as needed at any time during the data review and cleaning.

Schedule of upcoming EDSMC meetings for the CCPPP:

December 2, 2005 – Conference Call

April/May 2006 – Meeting in Tucson, Arizona

December 2006 – Conference Call

April/May 2007 – Meeting in Tucson, Arizona

December 2007 – Conference Call

April/May 2008 – Meeting in Tucson, Arizona

December 2008 – Conference Call

April/May 2009 – Meeting in Tucson, Arizona

(Initial Data and Safety Monitoring Plan was approved by Winfred Malone, Ph.D., M.P.H. Program Director, National Institutes of Health, Chemoprevention Branch, Division of Cancer Prevention, January 2001; earlier draft of this revision approved December 2005)

APPENDIX 8: CTSA Confidentiality and Data Sharing Agreements

CONFIDENTIAL DISCLOSURE AGREEMENT Cross Trial Safety Analysis (CTSA)

This Agreement is made by and between the **National Cancer Institute** (hereinafter referred to as "NCI"), an agency of the United States Government, and _____, an entity organized and existing under the laws of _____ (hereinafter referred to as "Entity"). Collectively or individually, the NCI and Entity shall also be referred to as "Parties" or "Party."

WHEREAS, Entity has certain confidential information relating to the attached Cross Trial Safety Analysis Statement of Intent (hereinafter referred to as the "Confidential Information"); and

WHEREAS, the NCI is interested in obtaining the Confidential Information for use in a cross trial safety analysis, as described in the attached Cross Trial Safety Analysis Statement of Intent (the "Purpose");

NOW, THEREFORE, in consideration of the promises and mutual covenants contained herein, the Parties hereto agree as follows:

1. Entity shall disclose and transmit Confidential Information to the NCI for the Purpose.
2. The NCI agrees to accept the Confidential Information and employ all reasonable efforts to maintain the Confidential Information of Entity secret and confidential, such efforts to be no less than the degree of care employed by the NCI to preserve and safeguard its own confidential information. The Confidential Information shall not be disclosed, revealed, or given to anyone by the NCI except employees or contractors of the NCI who have a need for the Confidential Information in connection with the Purpose, and such employees or contractors shall be advised by the NCI of the confidential nature of the Confidential Information and that the Confidential Information shall be treated accordingly.
3. The Entity hereby acknowledges that the NCI shall not incur any liability merely for examining and considering the Confidential Information; however, the NCI agrees that it will not use the Confidential Information for any purpose except as set forth herein.
4. The NCI's obligations under Paragraph 2 and 3 above shall not extend to any part of the Confidential Information of the Entity:
 - (a) that can be demonstrated to have been in the public domain or publicly known at the time of disclosure; or
 - (b) that can be demonstrated to have been in the NCI's possession or that can be demonstrated to have been readily available to the NCI from another source prior to the disclosure; or

(c) that becomes part of the public domain or publicly known by publication or otherwise, not due to any unauthorized act by the NCI; or

(d) that can be demonstrated as independently developed or acquired by the NCI without reference to or reliance upon such Confidential Information; or

(e) that is required to be disclosed by law.

5. The NCI's obligations under Paragraphs 2 and 3 shall extend for a period of three (3) years from the date of this Agreement, unless Entity informs the NCI that the Confidential Information is still secret and confidential, in which case the obligations of Paragraphs 2 and 3 hereof shall extend for a further period of two (2) additional years.
6. All information to be deemed confidential under this Agreement shall be clearly marked "**CONFIDENTIAL**" by Entity. Any Confidential Information which is orally disclosed must be reduced to writing and marked "**CONFIDENTIAL**" by Entity and such notice must be provided to the NCI within thirty (30) days of such disclosure.
7. It is understood that nothing herein shall be deemed to constitute, by implication or otherwise, the grant to the NCI of any license or other rights under any patent, patent application or other intellectual property right or interest belonging to Entity.
8. It is understood and agreed by both Parties that each represents and warrants to the other Party that each Official signing this Agreement has authority to do so.
9. The illegality or invalidity of any provision of this Agreement shall not impair, affect or invalidate the other provisions of this Agreement.
10. The construction, validity, performance and effect of this Agreement shall be governed by Federal law, as applied by the Federal Courts in the District of Columbia.

SIGNATURES BEGIN ON THE FOLLOWING PAGE

ACCEPTED AND AGREED

The undersigned expressly certify or affirm that the contents of any statements made or reflected in this document are truthful and accurate. The undersigned further agree to examine and consider the subject matter of the Confidential Information on the foregoing basis.

FOR THE NATIONAL CANCER INSTITUTE (NCI)

(Authorized Signatory for NCI)

Date

Laurie Ward Whitney, Ph.D.
Technology Transfer Specialist
National Cancer Institute
National Institutes of Health
6120 Executive Blvd, Suite 450
Rockville, MD 20892

FOR THE ENTITY

(Authorized Signatory for Entity)

Date

(Printed Name)

(Title of Signatory)

Address:

Cross Trial Safety Analysis (CTSA) Statement of Intent

A. CTSA BACKGROUND & RATIONALE

1. The withdrawal of rofecoxib (Vioxx[®]) from the market in the fall of 2004 and recently published safety data from the Adenoma Prevention with Celecoxib (APC) Trial have raised questions concerning the safety of the class of COX-2 inhibitors
2. Decisions to suspend or stop several celecoxib (Celebrex[®]) prevention trials (or the use of celecoxib on certain trials) late in 2004 because of an apparent excess of cardio- and cerebrovascular events in those trials has served to underscore those concerns
3. A better understanding of the risk profile of celecoxib is of public health import
4. Recently completed and on-going long-term randomized, placebo-controlled, prevention trials contain information bearing on the cardio- and cerebrovascular risk profile of celecoxib
5. A pooled analysis of comparable data from several trials is likely to provide a more reliable estimate of risk than safety data obtained from any single trial

These things being so, the parties and persons represented by signatures below intend to adjudicate and pool cardio-and cerebrovascular event data emerging from their celecoxib prevention trials (in addition to ancillary information required for the successful execution of this effort) for analysis in a collaborative effort, herein referred to as the Cross Trials Safety Analysis (CTSA).

B. CTSA COLLABORATORS

The CTSA will collect, adjudicate, and analyze data arising from selected randomized, parallel, placebo-controlled, trials of celecoxib as outlined below and detailed in the CTSA Protocol for a pooled analysis.

1. Individual Study Principal Investigators
 - Bertagnolli: Adenoma Prevention with Celecoxib (APC) Trial
 - Levin: Prevention of Sporadic Adenomatous Polyps (PreSAP) Trial
 - Breitner: Alzheimers Disease Antiinflammatory Prevention Trial (ADAPT)
 - Goss: Randomized Phase III Trial of Exemestane vs Anastrozole with or without Celecoxib in Postmenopausal Women with Receptor Positive Primary Breast Cancer (MA-27 Trial)
 - Lance: (Sel-Cel Trial)
 - Chew: Preliminary Multi-Center Assessment of Laser and Medical Treatment of Diabetic Macular Edema (NEI Trial)
2. Individual Trial Sponsors
 - National Cancer Institute, Division of Cancer Prevention (NCI, DCP)
 - National Cancer Institute, Division of Cancer Treatment and Diagnosis (NCI, DCTD)
 - National Cancer Institute of Canada (NCI Canada)
 - National Eye Institute (NEI)
 - National Institute on Aging (NIA)
 - Pfizer, Inc.

3. CTSA Working Group (WG)

- Event Adjudication Center – EAC (Brigham and Women’s Hospital; Boston, MA)
- Data Analysis Center – DAC (Statistics Collaborative, Inc, Washington, DC)
- Project Office – PO (NCI; Bethesda)

C. COLLABORATOR ROLES

Materials supplied by representatives of sponsors/trials eligible for inclusion in the CTSA include but are not limited to the following:

- Final or most recent version of the study protocol and study manual (when the latter exists)
- Copies of blank case report forms (CRFs)
- Raw counts of persons randomized by treatment group, person years of follow-up per treatment group (as defined by assignment), and events as classified per the CTSA Protocol
- Data sets sufficient to perform analyses of individual patient data (IPD) as specified in the CTSA Protocol; said data sets are to include treatment assignment and baseline data sufficient to characterize the study population and to carry out subgroup analyses for selected baseline characteristics as specified by the CTSA DAC

Materials supplied by the EAC include but are not limited to the following:

- CTSA standardized protocol for the collection, blinded adjudication, and compilation of serious cardio- and cerebrovascular event (including deaths) occurring on CTSA trials
- Delivery of adjudicated cardio- and cerebrovascular event data to the DAC

Materials supplied by the DAC include but are not limited to the following:

- CTSA Data Analysis Plan
- CTSA pooled analysis

D. CTSA DECISION-MAKING BODIES/PROCESS

Responsibility for leadership and overall direction of the CTSA shall be vested in the CTSA Steering Committee (SC), which is comprised of one representative from each collaborator, as defined in Section B (above). A second person, eligible to stand in and vote in the absence of the SC designee may also be designated. The SC will be co-chaired by the DAC and EAC Directors. The SC shall be the final authority in establishing and maintaining the CTSA Protocol and shall be the sole and final sign-off authority on the manuscript or manuscripts containing the principal results of the CTSA (i.e., related to the pooled analyses). The publication/presentation of adjudicated cardio- and cerebrovascular event analyses arising from each trial, however, will be the purview of each trial’s investigator, sponsor and the CTSA WG.

The SC will meet by conference call or face-to-face, as determined by the NCI and SC Chairs. A quorum for conduct of business shall be at least one of the SC Chairs and a majority of SC members. However, there shall be at least two face-to-face meetings over the course of the CTSA. One meeting shall take place prior to approval of the CTSA Protocol. Another shall take place when the pooled analysis is complete as a prelude to manuscript production and submission.

A second body, herein referred to as the CTSA Working Group (WG), shall be responsible for day-to-day direction and operation, and for ensuring proper CTSA conduct and execution. The WG shall be

comprised of the NCI CTSA Project Officer, and the DAC and EAC Directors. Meetings will be via conference call or face-to-face when deemed necessary or appropriate.

The CTSA Protocol shall be developed by the WG, and will be submitted to the SC for approval. Major amendments to the Protocol during the CTSA, should they be necessary, will likewise be subject to review and approval by the SC.

E. PUBLICATIONS/PRESENTATIONS

The primary products of the CTSA shall be adjudicated cardiovascular and cerebrovascular event analyses arising from each trial, as well a pooled analysis of patient level data. These data are expected to be published in peer-reviewed indexed journals. The SC will be responsible for sign-off on principal manuscripts prior to journal submission. Sponsoring agencies of trials represented in the CTSA will have right of review, but the final say regarding publication content and conclusion(s) will rest with the SC.

F. AUTHORSHIP OPTIONS

- a) Conventional format
Masthead lists individual authors as determined by the WC, which will be designated by the SC
- b) Modified conventional format
Masthead lists individual authors followed by “for The Cross Trials Safety Analysis Research Group” (as determined by the WC)
- c) Corporate format
Masthead lists the Cross Trials Safety Analysis Research Group plus a full credit listing identifying all participating trials and sponsoring agencies, but absent any listing indicating the WC responsible for producing the manuscript (revealed only to the journal editor to satisfy journal authenticity requirements).
- d) Modified corporate format
Masthead lists the Cross Trials Safety Analysis Research Group plus a listing of the WC, the order of authors is listed in a footnote

Having read and subscribing to principles and practices set-forth in this Cross Trial Safety Analysis Statement of Intent, we, the undersigned, agree to be a collaborating partner in the CTSA and in so doing agree to provide information specified in the CTSA Protocol and to answering questions and queries regarding this trial from the DAC and EAC in relation to pooling safety data from celecoxib prevention trials.

Signature	Date	Title/affiliation
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

(Thu 10:24am) 30 Jun 05